1989

Chapter I. The synthesis, conformational analysis and catalytic properties of four chiral (non-racemic) 4-substituted quinolizidines. Chapter II. Alkylation reactions of derivatives of the camphor-imine of t-butyl-glycine.

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University of Windsor

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CHAPTER I - THE SYNTHESIS, CONFORMATIONAL ANALYSIS AND CATALYTIC PROPERTIES OF FOUR CHIRAL (NON-RACEMIC) 4-SUBSTITUTED QUINOLIZIDINES.

CHAPTER II - ALKYLATION REACTIONS OF DERIVATIVES OF THE CAMPHOR IMINE OF t-BUTYLGLYCINE.

BY

© LUCA CARMINE MATASSA

A Dissertation

Submitted to the Faculty of Graduate Studies through the Department of Chemistry and Biochemistry in partial fulfillment of the requirements for the Degree of Doctor of Philosophy at The University of Windsor

1989

ISBN 0-315-50520-6

PAGE 7016

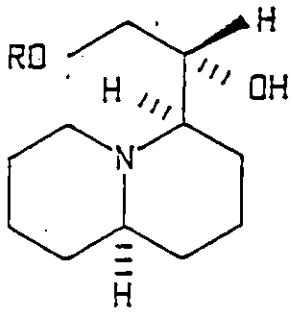
ABSTRACT

CHAPTER I

The Synthesis, Conformational Analysis and Catalytic Properties of Four Chiral (non-racemic) 4-substituted Quinolizidines.

The synthesis of 4R, 10R, 11R and 4S, 10R, 11S 4-[1-hydroxy-2-(benzyloxy)ethyl]quinolizidine (76a and 76b); and 4-(1,2-dihydroxyethyl)quinolizidine (78a and 78b) in enantiomerically pure form has been achieved. The chiral centers were established by formation of a chiral 2-substituted piperidine and cyclization of optically active epoxides. The solution conformation of these molecules (shown below) have been determined by 300 MHz proton NMR measurements. Amino alcohols 76a and 78a were found to exist in a trans-fused 6,6 ring junction whereas 76b and 78b were found to exist in a cis-fused 6,6 ring junction.

The metal salts of diastereomeric quinolizidines 76a/76b and 78a/78b function as catalysts, providing opposing enantioselectivity in the diethyl zinc addition to benzaldehyde. Both 76a and 78a gave the S enantiomer of 1-phenyl-1-propanol in excess while 76b and 78b gave the R enantiomer in excess. The best result was obtained employing the lithium salt of 76a as a catalyst which produced a 98% chemical yield of S enantiomer in 84% enantiomeric excess. The R enantiomer was obtained in 58% enantiomeric exccess and in 76% chemical yield employing the zinc salt of amino alcohol 78b as the catalyst.



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10R

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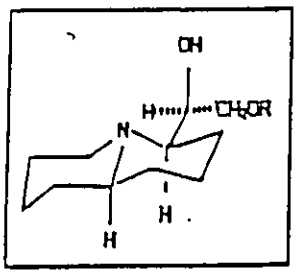
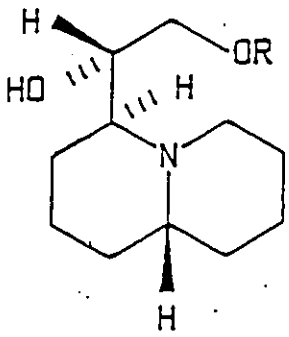
78a R = H



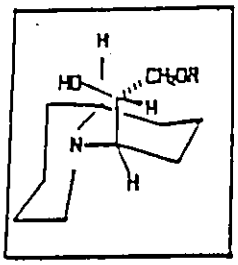


4S 11S

10R

76a R = Bn

78b R = H



ABSTRACT

CHAPTER II

Alkylation Reactions of Derivatives of the Camphor Imine of t-Butylglycine.

The norcamphor imine of t-butylglycinate was prepared and found to exist as a 5:1 ratio of geometric isomers at the imine double bond. Alkylation reactions of the corresponding lithium enolate with benzyl bromide proceed with no diastereofacial selectivity implying that the methyl groups are crucial to obtaining high diastereofacial selectivity in the corresponding camphor imine.

The 10-hydroxymethylcamphor imine of t-butyl glycinate was prepared and found to exist as a single diastereomer at the imine double bond. Alkylation reactions of the corresponding dilithium enolate with benzyl bromide were found to give products with lower diastereofacial selectivity (de = 80%) compared to the corresponding camphor imine (de = 100%). Addition of hexamethyl phosphoramide caused an increase in the chemical yield but had little effect on the diastereofacial selectivity.

This 10-hydroxymethylcamphor imine also undergoes aldol reaction with benzaldehyde.

For Tammy

and

my parents.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my research supervisor Dr. John M. McIntosh. Both his thoughtful guidance and financial support will not be forgotten.

I would like to acknowledge my lab mates; both past and present. Their sincere interest in my well-being is appreciated. I would like to acknowledge the support of the technical staff (especially Mr. Mike Fuerth) for their assistance in obtaining spectral data and Dr. R. D. Bach (Wayne State University) who generously provided the facilities for obtaining optical rotations. Dr. C. Rogers (Bruker Spectrospin) kindly provided the C-H correlated NMR spectra before our facilities became available.

I am most grateful to my future wife, Tammy Lee Sartor, for her tireless commitment in typing this thesis and her unending support.

The financial support of the University of Windsor in the form of a teaching assistantship is also acknowledged.

Many thanks go to my family, especially my parents, for their moral support and guidance in making all of this possible. Thanks mom and dad!

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LIST OF ABBREVIATIONS

Ac	acetate
Ar	aromatic
Bn	benzyl
Br	bromide
COD	cycloooctadiene
DME	1,2-dimethoxyethane
I	iodide
Me	methyl
MTPA	methoxytrifluoromethylphenylacetic acid
MVK	methyl vinyl ketone
NMO	N-methylmorpholine oxide
Ph	phenyl
PTC	phase transfer catalysis
Py	pyridine
TFa	trifluoroacetate

CHAPTER I

The Synthesis, Conformation Analysis and Catalytic Properties of Four Chiral (non-racemic) 4-Substituted Quinolizidines.

INTRODUCTION

Chiral beta-amino alcohols are important and interesting molecules. In addition to their important biological activities (e.g. quinine and ephedrine), some have been employed successfully as chiral directing agents in organic synthesis.[1] Perhaps their most attractive property is their propensity to function as asymmetric catalysts in several reactions.

Catalytic asymmetric synthesis is arguably the best route for the preparation of pure enantiomers starting from prochiral starting materials. The amount of chiral reagent required is small relative to the number of molecules synthesized, and by its nature the catalyst does not remain bound to the optically active product.

The term catalyst is usually understood to mean an agent which becomes involved in the reaction pathway in such a way that it lowers the activation energy and thus increases the reaction rate without itself becoming consumed. However, an agent may change an aspect of the reaction (e.g. its stereochemistry) by decelerating the rate of compet-

ing reactions. For example, selective formation of one enantiomer of a pair (asymmetric synthesis) may occur by acceleration of the rate of formation of one enantiomer or decelerating the rate of formation of the other. The result is a change in the stereochemical composition of the product without necessarily changing the overall rate of reaction. Such agents are commonly referred to as catalysts although they do not truly fit the usual definition given above. In this dissertation, this accepted usage of the term "catalyst" will be adopted.

The terms catalyst and catalytic quantities should not be confused. The definition of catalyst makes no reference to the amount of agent required. Thus, agents which cause the (e.g. stereochemical) effects only when they are present in stoichiometric amounts can still be considered catalysts. In this dissertation, the term "catalytic quantities" will be used to denote sub-stoichiometric amounts of the agent.

Success in asymmetric catalysis, like asymmetric synthesis in general, depends on a free energy difference, $\Delta\Delta G$, between diastereomeric transition states. (Figure 1.) Only when a chiral influence (X*, Figure 2) is present can diastereomeric transition states occur during the formation of a new chiral center. If no chiral influence is present then the transition states are enantiomeric and therefore of equal energy, in which case no difference in activation energy is present and no asymmetric synthesis is possible (assuming an achiral environment). When the chiral influence present is a catalyst, differentiation between the energies of the diastereomeric transition states occurs as a result of interactions between the catalyst, the substrate, and the reagent. Newly created chiral centers can then be formed in unequal amounts. The closer and stronger the interaction of the chiral catalyst with these

centers at the transition state, the greater $\Delta\Delta G$ becomes and consequently the higher the expected stereodifferentiation. For example when $\Delta\Delta G$ approaches 2 kcal/mol a product ratio of 96:4 will be obtained.[2] The term percent enantiomeric (or diastereomeric) excess (% ee, % de) is used to express the ratio of enantiomers (or diastereomers) and is calculated as follows:

$$\%ee = \frac{100 \times (\text{amount enantiomer A} - \text{amount enantiomer B})}{(\text{amount enantiomer A} + \text{amount enantiomer B})}$$

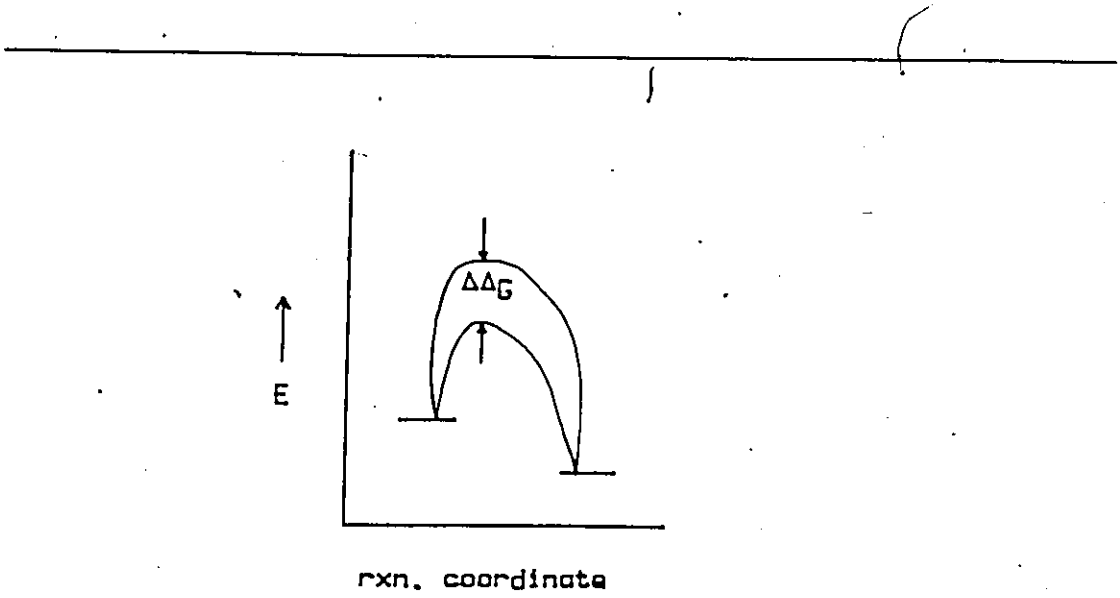


FIGURE 1. Energy diagram for an asymmetric reaction.

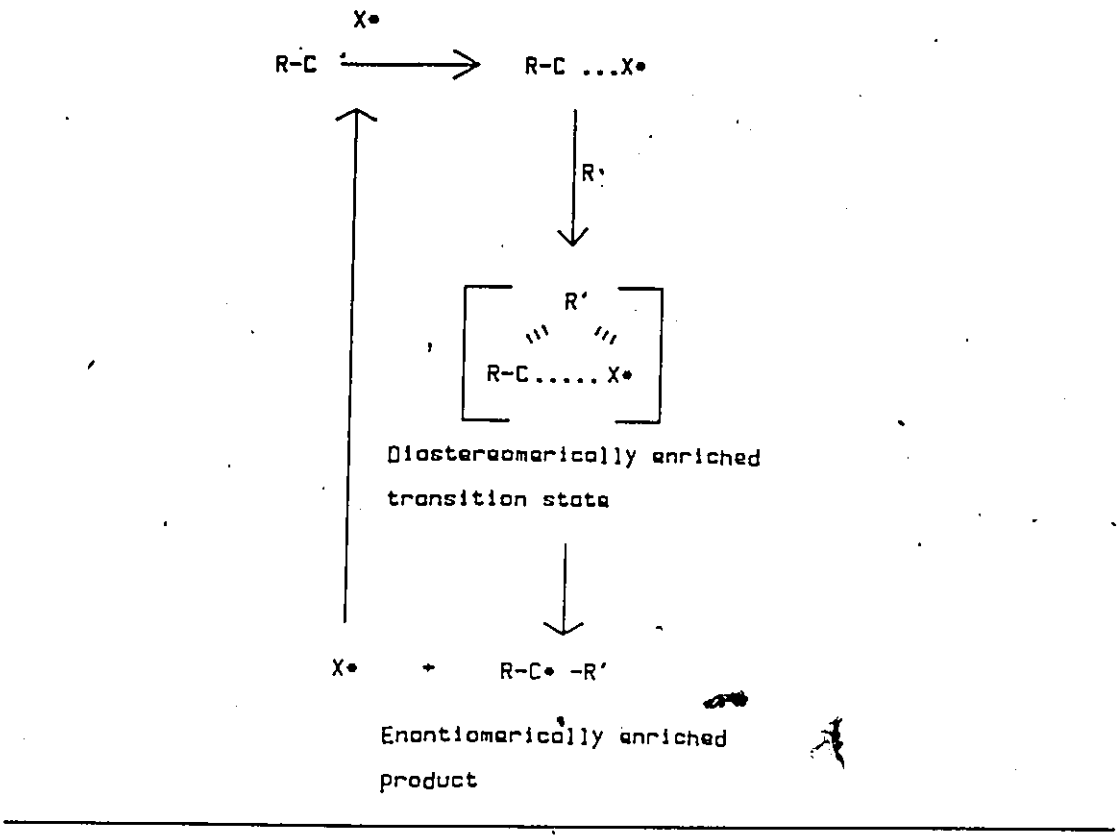


FIGURE 2. Catalytic cycle for asymmetric catalysis.

In order for a reaction to be considered synthetically useful, an ee (de) of greater than 90% is required. The process of asymmetric catalysis is depicted in Figure 2.

A plethora of papers describing the use of beta-amino alcohols as chiral catalysts in a number of transformations is present in the literature.[2-34] Several papers have been published reviewing early advances in this area.[2,3a] The evolution of the state of the art of asymmetric catalysis is revealed in reading these papers. Clearly any attempt to summarize this evolution is beyond the scope of this dissertation, therefore only a selection of the most recent and most promising examples will be presented.

The use of chiral beta-amino alcohols as catalysts can be catagorized as follows:

1. Enantioselective borane reductions of ketones catalyzed by chiral oxazaborolidines.
2. Enantioselective addition of dialkylzinc to aldehydes.
3. Asymmetric Michael Reactions.
4. Asymmetric 1, 4-additions to enones.
5. Asymmetric dihydroxylation reaction.
6. Asymmetric Phase Transfer Reactions.

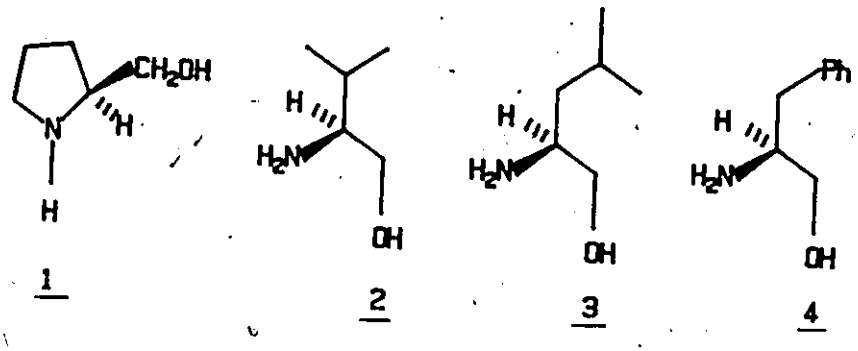
1. Enantioselective borane reductions of ketones catalyzed by chiral oxazaborolidines.

Itsuno[4], *et al.*, have developed an asymmetric reduction of aromatic ketones with reagents prepared from chiral beta-amino alcohols and borane. Employing 1-4 (Figure 3) as the chiral influences gave secondary alcohols with up to 60% enantioselectivity. The amino alcohols (1 equivalent) reacted with borane (2.5 equivalent) liberating 1 equivalent hydrogen and forming the "reducing mixture" which contained the alkoxyamine-borane complex. The importance of the hydroxy moiety was proven by utilizing the methyl ether of 1 and observing a decrease in ee from 44 to 16%.[4]

A significant improvement in the stereoselectivity of the reaction, (up to 100% ee) was reported in 1983 when 1 equivalent of the beta-amino alcohol 5 (Figure 4) was employed with a number of aromatic ketones.[5] Aliphatic ketones gave lower stereoselectivity (55-78%).[6] No explanation of the observed stereoselectivity in these reductions was given.

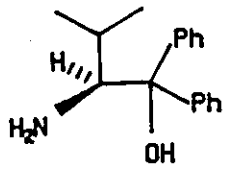
Polymer supported catalysts (example 6, ee's up to 80%) can be

used in batch type reactions[7] and continuous flow systems[8] (employing Z, ee's up to 90%). (Figure 5)



1 2 3 4

FIGURE 3. Chiral beta aminoalcohols employed for the asymmetric reduction of ketones by borane.[4]



5

FIGURE 4. Chiral aminoalcohol employed for the enantioseleective reduction of ketones by borane.[5]

Although considerable enantioselectivity was achieved in these reductions, a stoichiometric amount of chiral auxiliary was required. Most recently Itsuno has found[9] that a "white powder" of unknown composition could be isolated from the reaction of 5 with borane which in catalytic quantities accelerated the enantioselective reduction of

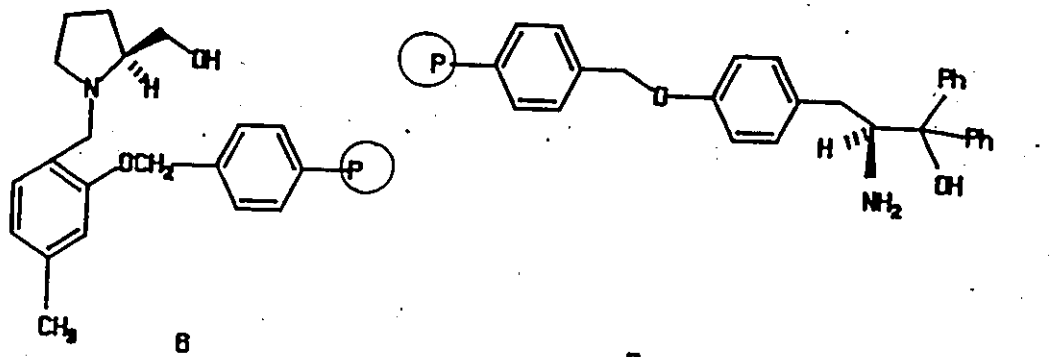


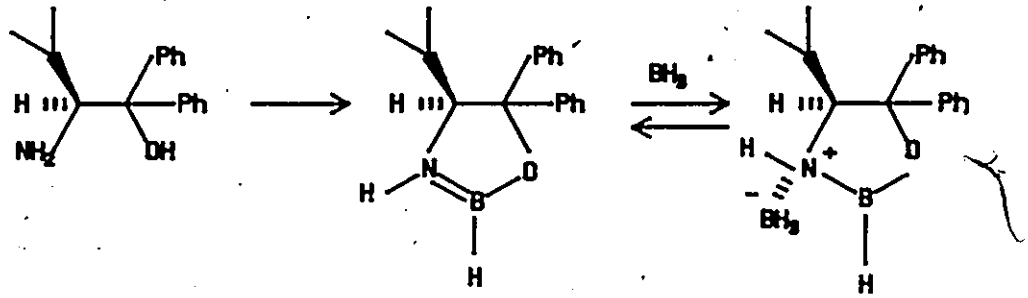
FIGURE 5. Polymer bound amino alcohols employed for asymmetric reduction of ketones by borane.[7,8]

acetophenone O-methyloxime to S-1-phenylethylamine by borane. The product was obtained in 80% yield and 95% enantiomeric excess. However, until further investigation has been carried out, no comment on the reagent structure, scope and mode of reduction can be made.

Corey's group has found that, only a catalytic amount of 8 (Figure 6) (.025 - .05 mol equiv.) was required to obtain good enantioselectivity in the borane reduction of aromatic ketones.[10] Further, it was demonstrated that the chiral oxazaborolidine 9 (derived from S-(-)-2-(diphenylhydroxymethyl) pyrrolidine and borane) (Figure 7) was even more effective and gave enantioselectivity equal to that achieved by Itsuno when used in catalytic quantities.[10]

These results shed light on the mechanism of this reduction. The 1:1 adduct shown in Figure 7, is perfectly structured so that coordination of the electrophilic ring boron with the ketonic oxygen (anti to the larger carbonyl appendage) and hydrogen transfer from the NBH^-_3 unit to the carbonyl carbon *via* a six membered cyclic transition state

provides the chiral secondary alcohols.



8

FIGURE 6. Catalyst responsible for asymmetric reduction of ketones by borane.[10]

The problems of air and moisture instability of 9 were overcome by employing the B-methylated oxazaborolidine[11] 10, (Figure 7) prepared by employing methyl boronic acid in place of borane. Oxazaborolidine 10 was as effective as 9 in enantioselective ketone reductions.

The synthetic power of this enantioselective reduction has been illustrated by a number of examples which include the synthesis of chiral phenyloxirane[11], prostaglandin[12], and other biologically active natural products.[13]

Pak, *et al.*,[14] have reported moderate to high enantioselectivity (46-97%) in the reduction of aliphatic and aromatic ketones employing one equivalent of the oxazaborolidine shown in Figure 8.

Interestingly, the enantioselectivity of the reduction decreased as the number of added equivalents of the oxazaborolidine decreased. For example, the enantioselectivity of the reduction of acetophenone decreased from 97 to 59 to 5% ee when 1, .1 and .025 eq of oxazaborolidine

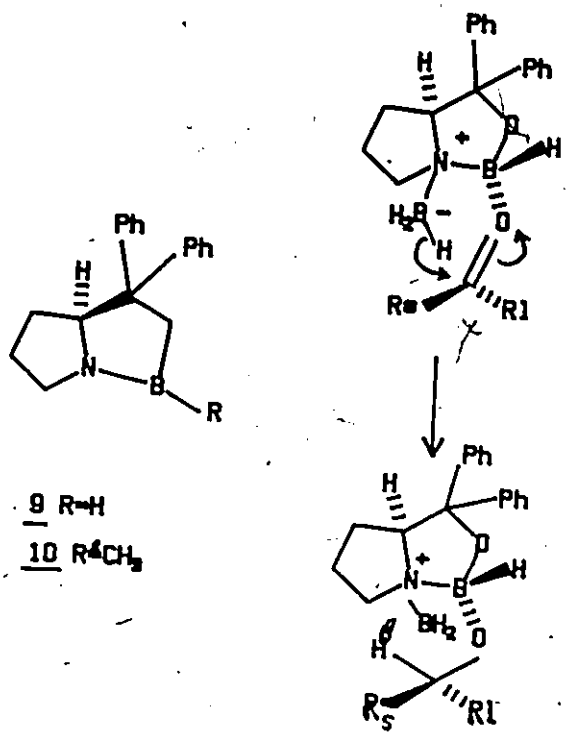


FIGURE 7. Corey's oxazaborolidine in the proposed mechanism of the asymmetric reduction of ketones by borane.[10,11]

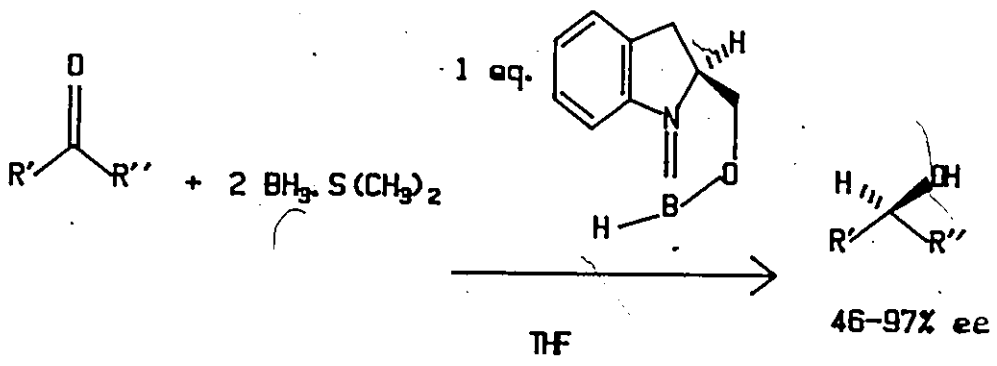


FIGURE 8. Pak's oxazaborolidine reduction.[14]

were employed respectively. The authors make no comment as to why this trend was observed, but it seems likely that the uncatalyzed reaction is competing successfully with the catalyzed one.

2. Enantioselective addition of dialkyl zincs to aldehydes in the presence of chiral amino alcohols.

The enantioselective addition of dialkyl zincs to various aldehydes catalyzed by various chiral beta-amino alcohols has been reported by several groups.[15-22] (Figure 9)

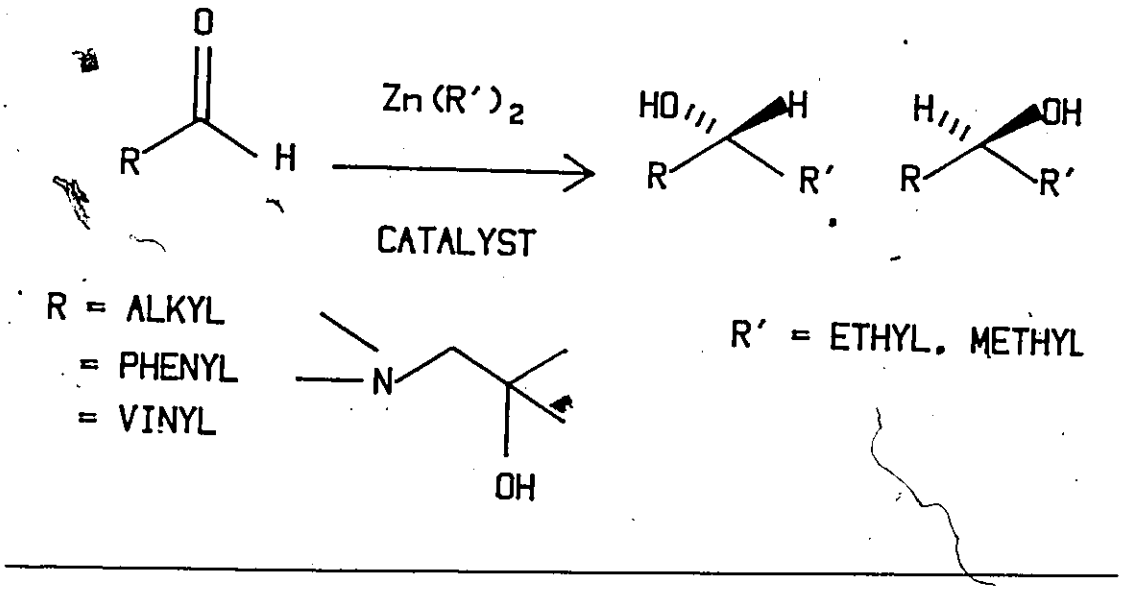


FIGURE 9. Addition of dialkyl zincs to aldehydes.

Optically active secondary alcohols are obtained in high chemical yields and enantioselectivities (up to 100%) under mild reaction conditions. The popularity of this reaction is due to several attractive features:

1. Only a truly catalytic amount (2-10 mol %) of chiral source is required for good asymmetric induction. It can be easily recovered in quantitative yield without racemization.

2. Alkyl, vinyl, and aryl aldehydes are alkylated with diethyl or dimethylzinc.

3. The reaction of $Zn(alkyl)_2$ with benzaldehyde is slow in the absence of catalyst at room temperature[19]. This avoids stereochemical dilution by the uncatalyzed reaction.

4. The reaction products are isolated easily and the stereoselectivity can be determined by several methods. Enantiomeric excesses of the secondary alcohol products may be determined directly by HPLC employing a chiral column[15a, 20] or by measurement of the optical rotation.[15a. d! 16-18] Integration of the capillary G. C.[15b, 16] or ^1H NMR of the Mosher ester[15b, d] or menthyloxycarbonyl derivative[16] of the secondary alcohols can also be employed to determine the stereoselectivity of the reaction.

Some of the more successful amino alcohols employed as catalysts for the diethylzinc addition to benzaldehyde are shown in Table 1 along with observed enantioselectivity. The table illustrates that excellent stereoselectivity for either enantiomer of 1-phenyl-1-propanol can be obtained depending on the choice of catalyst. Polymer bound catalysts have also been successfully employed in batch type reactions.[15c, 21]

Good enantioselectivity in the dialkylzinc addition to aliphatic aldehydes catalyzed by (1S, 2R)-(-)-2-(N, N-dibutylamino)-1-phenylpropan-1-ol (11) (Figure 10) has also been reported.[15d] Heptanal was ethylated in the presence of a catalytic amount (6 mol %) of 11 to give a 95% yield of S-nonan-3-ol in 88% ee. The dibutylamino moiety of 11 is essential for high enantioselectivity to be achieved with aliphatic aldehydes.

TABLE 1. Beta-amino alcohols used in the diethyl zinc addition to benzaldehyde.[15-22]

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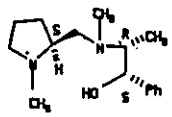
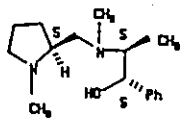
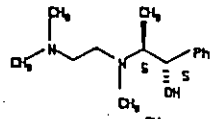
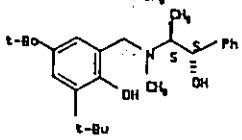
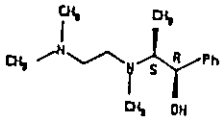
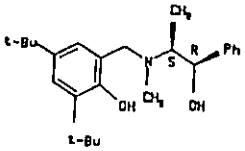
1	16		95	S
2			85	S
3			90	S
4			86	S
5			91	R
6			75	R
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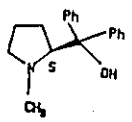
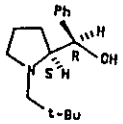
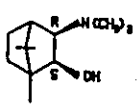
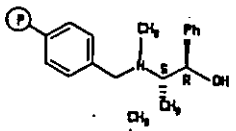
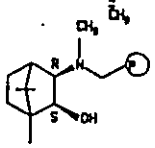
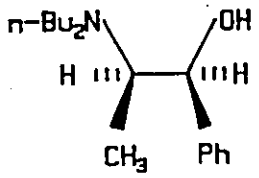
8		Quinidine	48	S
9		Cinchonidine	58	R
10		Cinchonine	46	S
11	15		100	S
12			100	R

13	20		99	S
14	15		89	R
15	21		92	S



11

FIGURE 10. Beta-aminoalcohol catalyst for dialkyl zinc addition to aliphatic aldehydes.[15d]

When the dimethyl analogue of 11 is employed the stereoselectivity in the ethylation of heptanal dropped (ee = 62%).

There is a striking correlation between the chirality at the alcohol stereocenter of the amino alcohol and the induced chirality in the predominant enantiomer formed. (See Table 1) The S stereocenter gives the S secondary alcohol in excess whereas the R stereocenter gives the R enantiomer in excess. The chirality at the alcohol stereocenter of the amino alcohol is largely responsible for the enantioselectivity of the catalyst, however the chiral center alpha to the nitrogen also contrib-

utes. Entries 1 and 2 of Table 1 reveal that employing amino alcohols which are enantiomeric at the chiral center alpha to the nitrogen but otherwise identical causes a 10% difference in the enantioselectivity. In the absence of a chiral alcohol stereocenter in the amino alcohol the chirality alpha to the nitrogen atom controls the stereoselectivity of the reaction (cf entry 11).

A mechanistic concept of the catalyzed reaction which is in accordance with this data is illustrated (Figure 11) for one amino alcohol (entry 1). This concept can be extended to the other amino alcohols as well. Complexation of benzaldehyde and diethyl zinc with the lithium (or zinc) salt of the amino alcohol *anti* to the steric bulk of the chiral auxilliary predicts preferential transfer of an ethyl group to the *si* face of the benzaldehyde to form the S-secondary alcohol, as observed.[16, 23] It is interesting to compare the intermediates in this cycle with the analogous intermediates in the catalyzed reduction presented earlier (Figure 7).

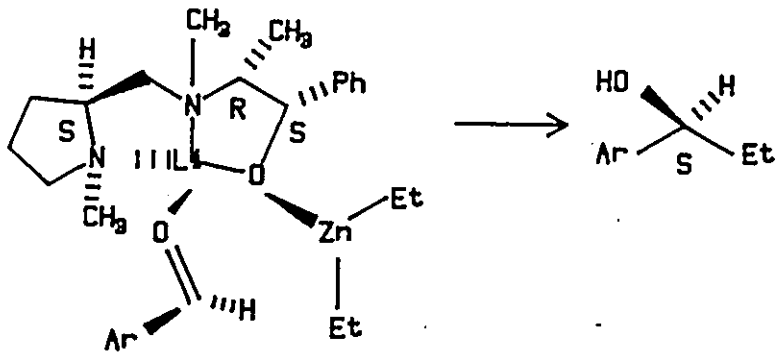


FIGURE 11. Mechanistic concept for the aminoalcohol catalyzed diethylzinc addition to benzaldehyde.[16]

It has been observed that reactions catalyzed by the lithium salt (prepared by adding an equimolar amount of n-BuLi to the amino alcohol) produces higher enantioselectivity than the corresponding zinc salt under otherwise identical conditions.[15a] Nonpolar and non-coordinating solvents (hexane, toluene) are superior to more polar solvent systems (Et_2O-hexane, THF) which retard the reaction and lower the enantioselectivity.[20] Lowering the temperature of the reaction has been found to slightly increase selectivity for simple amino alcohols. Surprisingly, the opposite has been found when cinchona alkaloids have been employed.[22]

3. Asymmetric Michael Reactions

Application of chiral beta-amino alcohols as catalysts in the Michael reaction has been reported. Intriguing examples of cinchona alkaloid catalyzed Michael addition reactions (Figure 12) have been reviewed by Wynberg.[3b]

A representative example can be found in the cinchona alkaloid catalyzed Michael addition of thiophenol to cyclohexenone. The results are illustrated in Table 2.

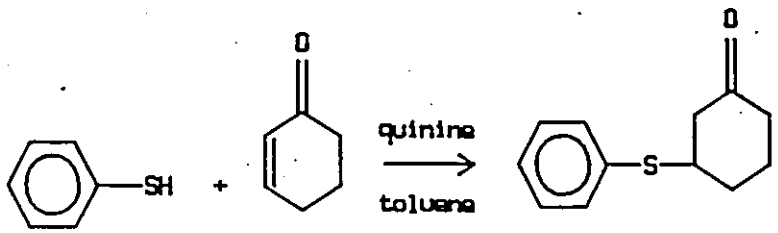
There are two key points to recognize:

1. A diastereomeric pair of alkaloids provides opposing enantioselectivity in the reaction products.

2. A diastereomeric pair of alkaloids gives a small but reproducible difference in the enantioselectivity of the reaction.

These facts can be rationalized as follows. Quinine and quinidine are diastereomers, as are cinchonidine and cinchonine. But, at the

TABLE 2. Cinchona alkaloids in the thiol addition reaction.[3]



e.e. 44%

Catalyst	Absolute configuration at C-8	Absolute configuration at C-9	Product Conf.	e.e.(%)
Quinine	S	R	R	44
Quinidine	R	S	S	55
Cinchonidine	S	R	R	62
Cinchonine	R	S	S	67

crucial catalytic sites - the amino alcohol portions of the alkaloids - they are enantiomeric. Therefore, if in an asymmetric transformation employing quinine as a chiral catalyst one enantiomer of the product is formed in excess, then the opposite enantiomer should be formed in excess when quinidine is used if the catalysts are truly inducing stereochemistry. This is the observed result. The same is true for cinchonidine and cinchonine, as is illustrated in table 2.

The observed correlation of product stereochemistry with absolute stereochemistry of the catalytically active portion of the catalyst is common to all reaction types (eg in the previously discussed reactions of diethylzinc table 1, entries 7-10). Enantiomerically related products are formed if the catalytic site is enantiomerically related even though

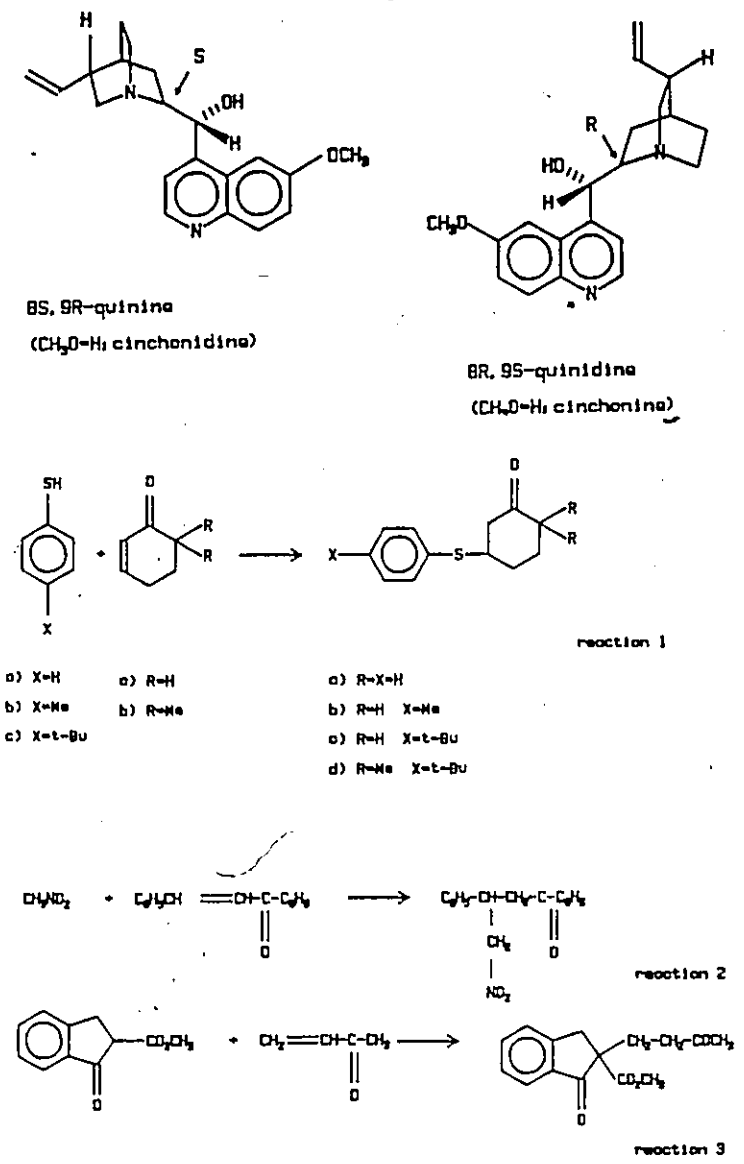


FIGURE 12. Cinchona alkaloid catalyzed Michael addition reactions.[24]

the whole catalyst structures are diastereomers of each other. If the whole catalyst structures had been enantiomerically related, opposing enantioselectivities in equal amounts and at equal reaction rates would be expected. Therefore, while the opposing enantioselecitivity between quinine and quinidine can be attributed to enantiomerically related

catalytic site, the difference in absolute values of the percent enantioselectivity and in the chemical yield must be attributed to the diastereomeric nature of the total molecules quinine and quinidine. The diastereomeric nature manifests itself *via* small but significant energy differences in the "best fits" of the respective transition states.[3a]

Sera, *et al.*[24] have determined that increasing pressure, while facilitating the reactions of type 2, decreases the enantioselectivity in the reactions 1-3 as expected. (Figure 12.) The observed decrease in the enantioselectivities by increasing pressure is explained by the effect of pressure on the two diastereomeric transition states leading to the enantiomeric products. The free energy difference, which occurs as a result of steric interactions will decrease as the pressure increases since increased pressure will partially overcome the steric interactions.

Indian workers[25] used the Michael addition of benzenethiol (12) to compound 13 catalyzed by quinine and quinidine in order to synthesize phenylalanine (16). (Figure 13) Under optimum conditions, a 70:30 mixture of R and S-phenylalanines (ie. ee = 40 %) was obtained from 15 after desulphurisation of 14.

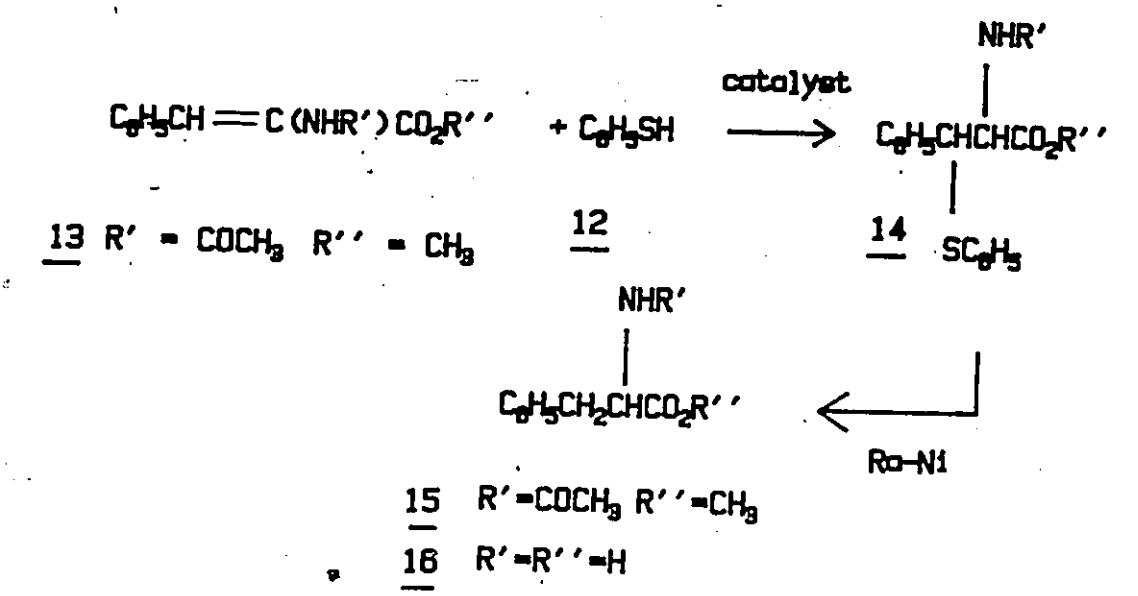


FIGURE 13. Phenylalanine synthesis *via* cinchona alkaloid catalyzed Michael addition.[25]

4. Asymmetric 1,4-addition to enones.

The first catalytic asymmetric conjugate addition of dialkylzinc reagents to acyclic alpha-beta unsaturated enones mediated by a nickel complex of chiral beta-amino alcohols (1S, 2R)-(-)-17 and (1R, 2S)-(+)-17 was recently reported.[26] (Figure 14)

The nickel complex, 18, prepared *in situ*, catalyzed conjugate addition of diethyl or dimethyl zinc to enones 19a-c with moderate enantioselectivity (depending on the molar ratio 18:19) and in yields ranging from 63 to 94% for 20a-d. For example the enantioselectivity of 20b increased from 20 to 45% as the molar ratio of 18:19 increased from 6 to 50%.

Recently Corey and coworkers[27] described effective chiral catalysts

for the enantioselective conjugate addition of organocopper reagents to cyclic alpha, beta-unsaturated enones. (Figure 15)

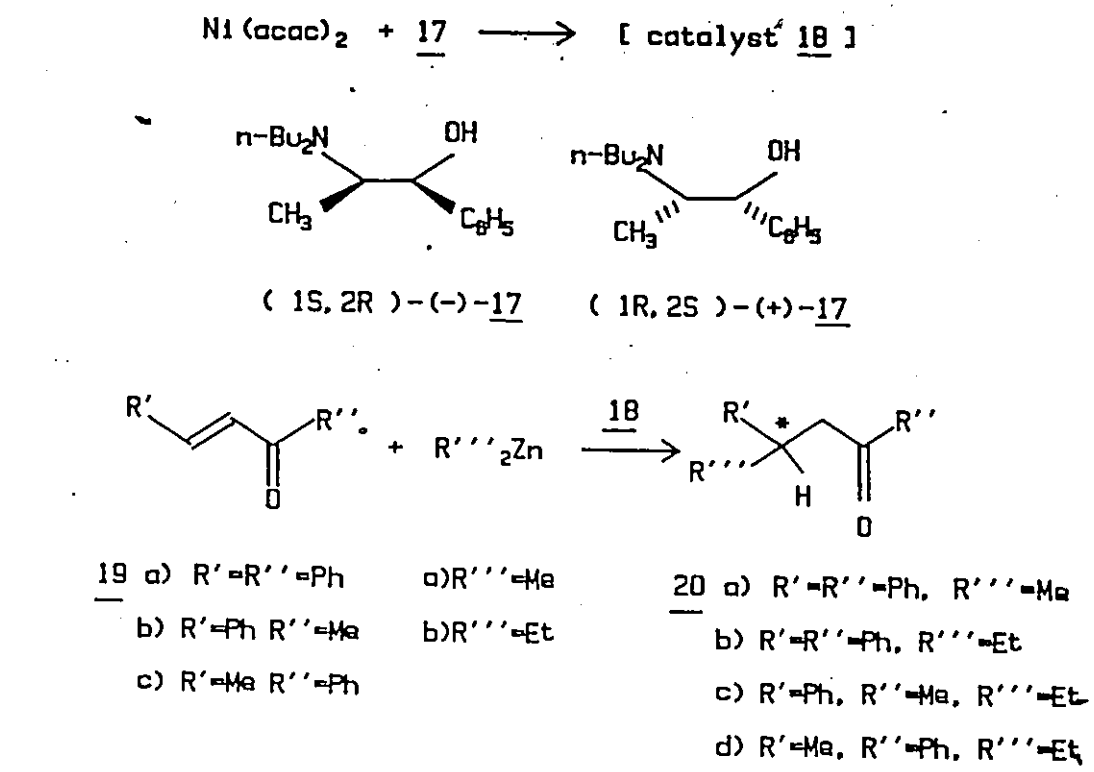


FIGURE 14. Conjugate addition to acyclic alpha,beta unsaturated enones.[26]

Lithiated 21 (prepared from 1R, 2S-(-)-ephedrine) combines 2-cyclohexenone and an organocopper reagent to selectively generate the addition product (eg. for R=C_2H_5 R(+), 92% ee). In the proposed mechanistic model the most reasonable modes of assembly of the substrate and catalyst, A and B both predict the same product stereochemistry, consequently no decision between these possibilities was made. Parallel experiments with 2-cyclopentenone gave similar stereochemical results and lower enantioselectivity than cyclohexenone (eg. R=C_2H_5, R(+), 77% ee).

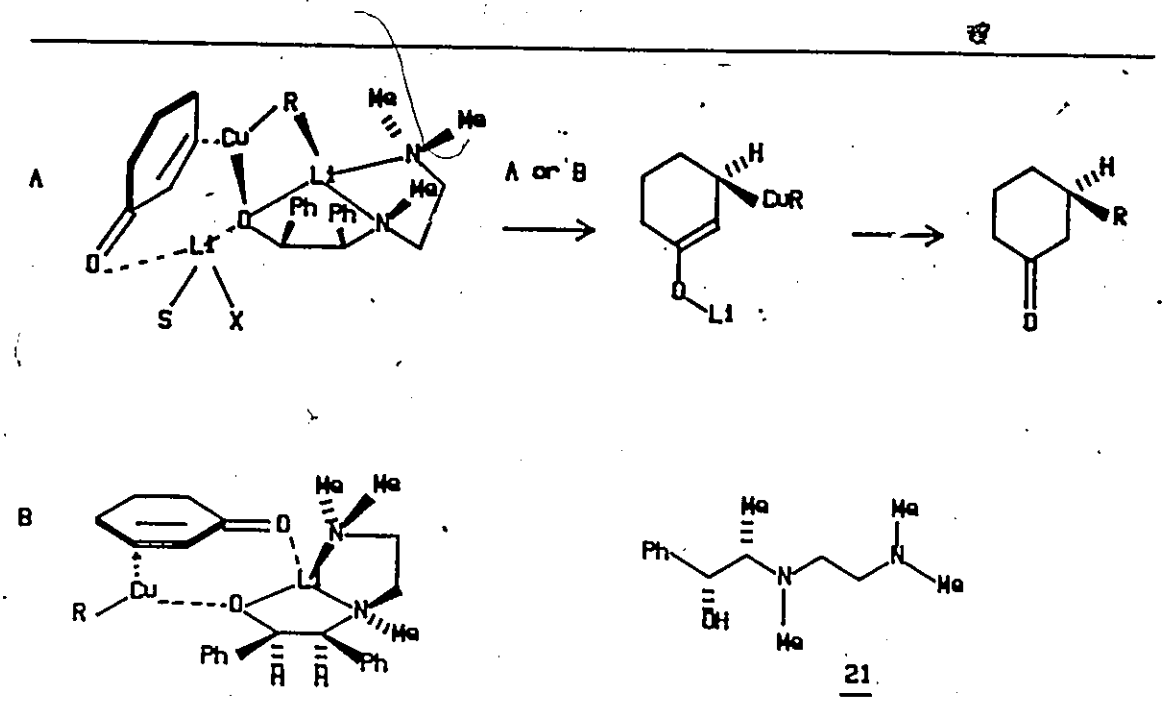


FIGURE 15. Mechanistic prroposal for the catalyzed conjugate addition of cuprates.[27]

5. Asymmetric Dihydroxylation Reaction

Modified cinchona alkaloids, quinine and quinidine have been utilized as ligands by Sharpless, *et al.*[28], in an enantioselective dihydroxylation of olefins with osmium tetroxide. (Figure 16). Noteworthy features of this reaction include; (1) no directing functional group required and therefore the reaction can be used with a large group of substrates; (2) these ligands accelerate the reaction and therefore very little catalyst is required; (3) the diastereomeric pair quinine and quinidine, which are enantiomeric at the catalytic sites, provide opposing enantioselectivity; (4) the reaction is insensitive to air, moisture and concentration effects which makes it easy to perform.

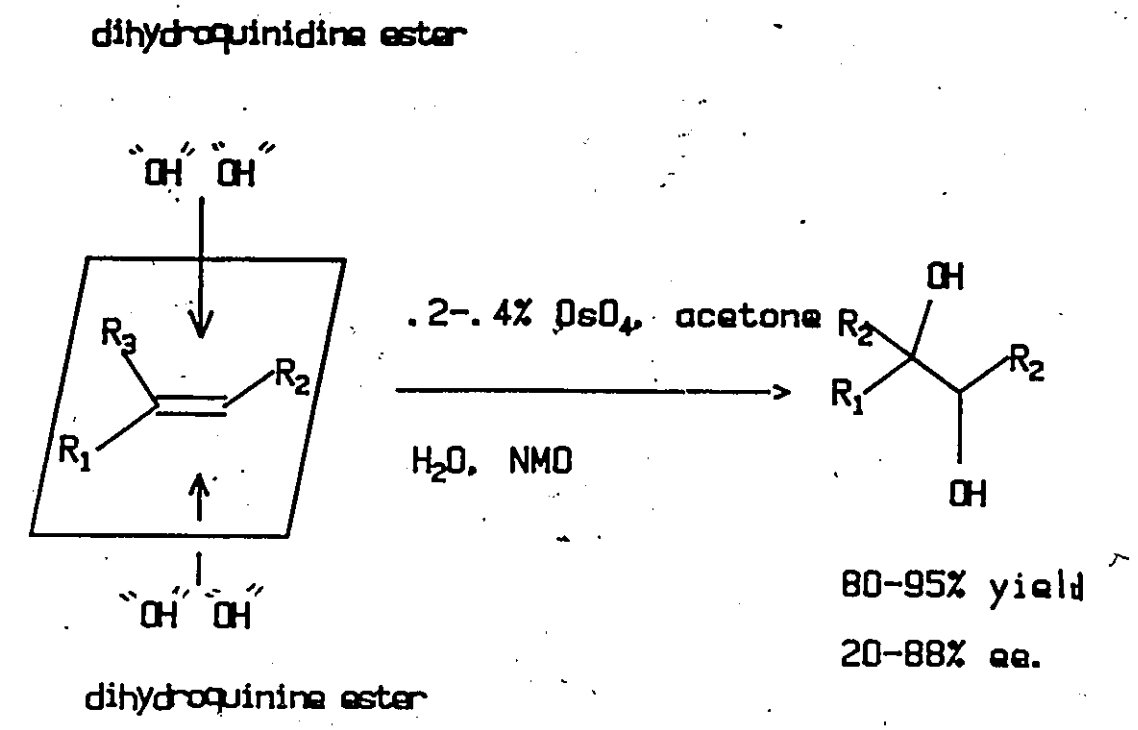


FIGURE 16. Asymmetric dihydroxylation of olefins.[28]

6. Asymmetric Phase Transfer Catalyzed (PTC) Reactions

Quaternization of the nitrogen atom of beta-hydroxy amines opens the door to their use in asymmetric PTC reactions. Phase transfer catalysis is applicable to reactions which are inhibited because of opposing solubility characteristics of the reactants. The ability of a small amount of the phase transfer agent (usually a quaternary ammonium salt) to solubilize anions in organic solvents by forming lipophilic ion pairs and the relatively lightly solvated nature of these ion pairs results in increased reaction rates. Optically active quaternary ammonium compounds have been used in various reactions in attempts to perform asymmetric synthesis under phase transfer conditions.

However, employing chiral quaternary ammonium compounds as phase transfer catalysts have usually led to very low enantioselectivities.[29] For example, McIntosh and Acquaah[30] prepared chiral 22 and 23 which gave good yields of products but enantioselectivities of less than 1% in the alkylation reaction shown. (Figure 17)

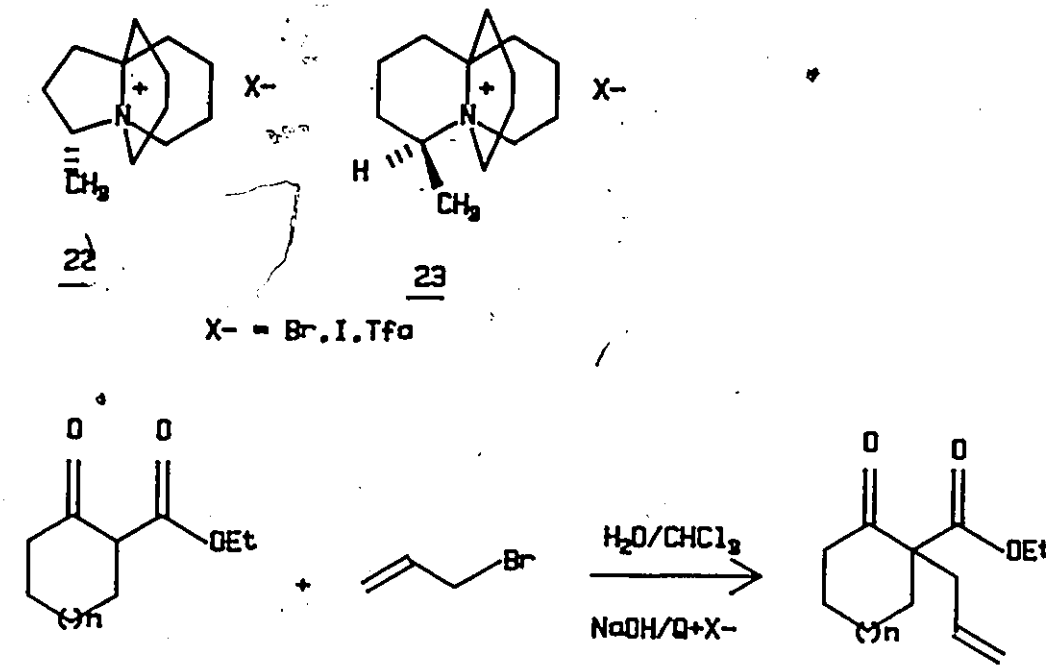


FIGURE 17. Alkylation reaction catalyzed by chiral ammonium salts.[30]

Much evidence has been accumulated showing that enantioselective phase transfer catalysis of reactions is successful only if there is multipoint interaction between the reacting species and catalyst in the transition state. Multipoint interactions "orient" the reacting species specifically for selective reaction.[31] Recognizing this point, early attempts at asymmetric phase transfer catalyzed reactions were made

employing chiral quaternary methylephedrine derivatives which contain a beta hydroxy group. Disappointingly low enantioselectivity was observed despite the presence of the hydroxy group. Eventually success was achieved employing the quaternized difunctional cinchona alkaloids.[29a]

Workers at Merck-Sharp reported the first efficient catalytic alkylation of a ketone. This was accomplished *via* asymmetric phase transfer catalysis mediated by substituted N-benzyl cinchoninium salts. Indanone 24 was converted to (S)-2-methyl analogue 25 in 94% ee and 98% yield[32] with N-[(p-trifluoromethyl benzyl)] cinchonium bromide (26) under phase transfer conditions. (Figure 18) Tight ion pairing between the catalyst and the substrate, (27) was invoked to account for the excellent enantioselectivity.

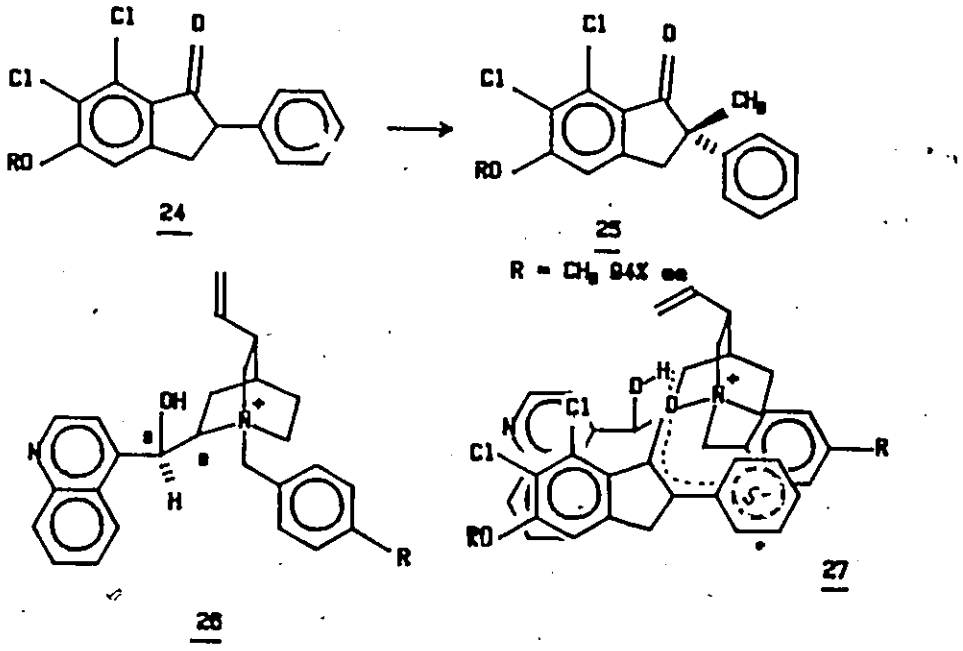


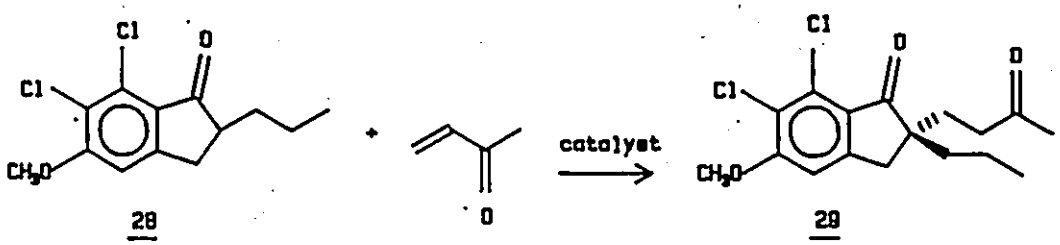
FIGURE 18. Stereoselective alkylation catalyzed by a N-benzylcinchonium salt.[32]

The quinoline ring, the C_9-O bond and the N-benzyl group all lie in one plane with the quinuclidine ring behind. The anion of 24 has almost a planar structure with the negative charge delocalized into the 2-phenyl ring. Both molecules, in their nearly planar conformations, fit naturally on top of each other providing a very specific π-interaction between the benzyl group of the catalyst and the 2-phenyl group of 24 on the one side and also between the beta hydroxy which provides a directional handle via hydrogen bonding to the indanone. The chloromethane can only alkylate from the front side leading to the observed product.[32] Reactions catalyzed by 6 mol% N-[p-(trifluoromethyl) benzyl] cinchonium bromide (26) gave the desired diketone 29 in 95% yield and 80% ee favouring the S enantiomer as predicted by the proposed ion pairing mechanism. Preparation of the R enantiomer employing (4-trifluoromethyl benzyl)-dihydrocinchonidium bromide 30 (R=Et, R_1=CF_3, R_2=H, X^-=Br) gave an excellent yield and an ee of 52%.

Shioiri has recently reported[34] the first catalytic enantioselective oxidation of achiral ketones with molecular oxygen by use of the chiral phase transfer catalyst N-[p-(trifluoromethyl benzyl] cinchonium bromide. (26, Figure 19). Alpha-hydroxy ketones, 32 (Figure 20), are obtained in greater than 90% yield and up to 79% enantiomeric excess from 31 (R_1=Cl, R_2=R_3=H, R_4=OCH_3, R_5=CH_3, n=2). In these reactions ion pairing between the catalyst and the ketone accounts for the enantioselectivity as previously described.

Surprisingly, little attention has been given to the possible use of pyrrolidine-derived amino alcohols as PTC's (ex. 9.) These were used effectively as BH_3 reduction catalysts and as $Zn(Et)_2$ addition catalysts. When similarily quaternized, they may also be effective chiral

phase transfer catalysts.



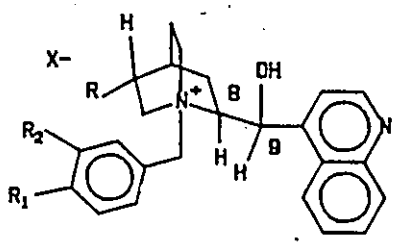


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FIGURE 19. MVK addition catalyzed by N-benzylcinchonium salt.[33]

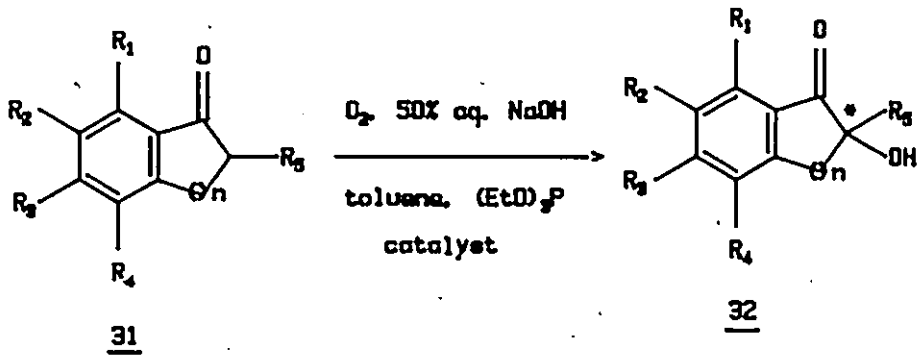


FIGURE 20. Alpha hydroxylation of ketones.[34]

While no single compound can catalyze and induce asymmetry effi-

ciently in every reaction, the examples presented illustrate the general utility of various chiral beta-amino alcohols in this regard. In general the success of beta-amino alcohols as asymmetric catalysts can be attributed to three factors. The first of these is the environment of the nitrogen atom. Chirality, and or steric bulk, adjacent to the nitrogen atom are important for effective chirality transfer in both the neutral and quaternized catalysts presented. The second factor is chirality in close proximity to the other catalytically active site of the molecule ie. the hydroxy portion. Finally, and perhaps most important is the difunctional nature of the chiral beta-aminoalcohols. Simple chiral amines and chiral alcohols[18,35], are not nearly as effective as enantioselective catalysts as the chiral beta-amino alcohols. The examples presented illustrate the powerful effects of the amine and the hydroxy groups, acting in concert, to achieve efficient chirality transfer.

Our objective was to determine the influence on the induced chirality transfer of changing the stereochemistry of the beta-aminoalcohol portions of the molecules which were to be used as catalysts. This objective required that we obtain a set of enantiomerically pure and stereoisomerically related molecules of this type of known configuration and conformation. These compounds might best be prepared by a synthetic route which relies upon the preparation of an intermediate common to both syntheses which could then be elaborated into the desired stereoisomers at the latest possible stage. The choice of the target molecules was influenced strongly by our previous experience[36] with the quinolizidine ring system. (Figure 21) In addition, conformational analysis of these systems undoubtedly will be important in rationalizing their

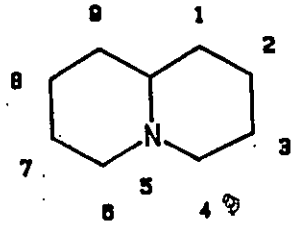


FIGURE 21. The quinolizidine ring system.

catalytic properties and chirality transfer. Previous workers[37] have shown that such information can readily be obtained from the proton NMR of the quinolizidine ring system and this prior experience was expected to be useful in obtaining the required conformational information.

We concentrated on the synthesis of two enantiomerically pure[38] diastereomers of each of two substituted quinolizidines shown in Figure 22 whose functionality makes them useful for catalytic purposes.

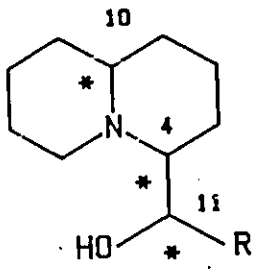


FIGURE 22. Target 4-substituted quinolizidine system.

The target molecules possess three chiral centers (C4, C10, C11). The synthesis, conformational analysis and catalytic properties of these two stereoisomers are outlined in subsequent chapters of this thesis.

Due to the possibility of inversion at the nitrogen atom, interesting conformational situations arise in the quinolizidine nucleus.[37] These are shown in Figure 23.

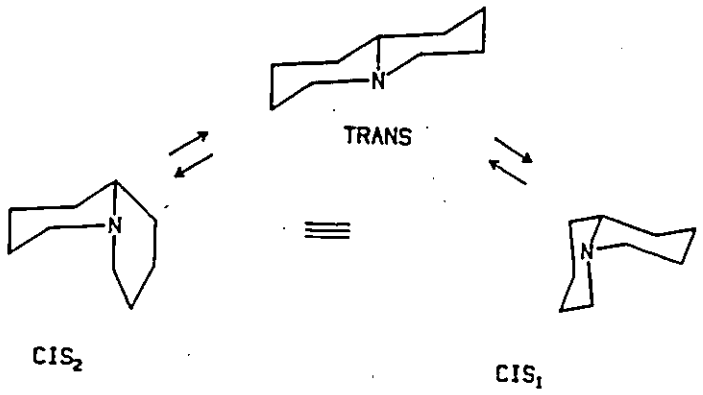


FIGURE 23. Conformational equilibrium in quinolizidine.

It is generally accepted that the conformational equilibrium in the unsubstituted quinolizidine ring system lies toward the trans conformation. Bohlmann[37a] has shown that a prominent infrared band at 2800-2700 cm^{-1} occurs in the spectra of trans-fused quinolizidines in which the nitrogen lone pair is trans and coplanar to at least two axial hydrogens on carbons adjacent to nitrogen. This band is absent in cis-quinolizidines where only one alpha-hydrogen is trans and coplanar to the N-lone pair.

The ^1H NMR spectra of quinolizidine has been examined and revealed a similar interaction. Protons immediately adjacent to nitrogen show characteristic chemical shifts depending on the dihedral angle between the proton and the nitrogen lone pair. An antiperiplanar alignment (180^o) causes an upfield shift (δ = .8 - 1.0 ppm) relative to protons

at angles of 60° and 120° which normally appear around 3 ppm.

Effects associated with the nitrogen and its lone pair on the ^{13}C NMR spectra quinolizidines are also apparent.[37b] Carbons alpha to the nitrogen are shifted downfield due to the inductive effect of the nitrogen relative to a decalin system. Further, an upfield shift occurs in the chemical shift of the alpha carbons of cis quinolizidines relative to trans quinolizidines.

The quinolizidine nucleus is found in several classes of interesting alkaloids. For this reason, most reported synthetic routes to the quinolizidine ring systems are contained in total syntheses of alkaloids. Historically, lupinine and epilupinine are the two quinolizidine ring-bearing alkaloid targets which have attracted the greatest attention. As such they will be the focus of this review of some recent literature methods for quinolizidine ring synthesis. The older methods utilized for lupinine and epilupinine synthesis have been reviewed.[39]

Building on their earlier results[40] for construction of quinolizidine alkaloids employing intramolecular immonium ion based Diels-Alder reaction, (Figure 24), Grieco, *et al.*, have recently reported[41] the total synthesis of racemic lupinine 38 and epilupinine (39).

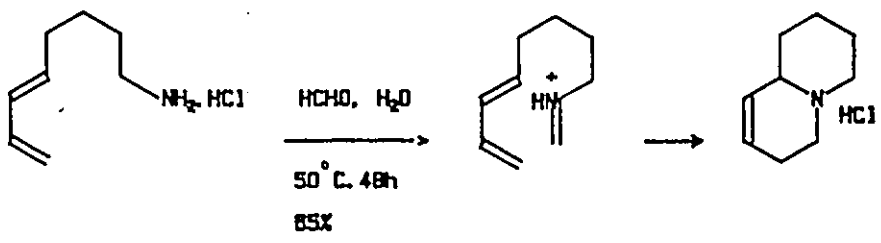


FIGURE 24. Intramolecular immonium ion-based Diels Alder reaction.[40]

Racemic 39 and 38 were obtained in 80% yield by reduction of readily separable Diels Alder adducts 34 and 35 which were derived from the iminium ion 33. (Figure 25) Interestingly, 34 and 35 were obtained in a 1.6:1 ratio a fact which was rationalized on the basis of chair-like transition states 36 and 37, respectively.

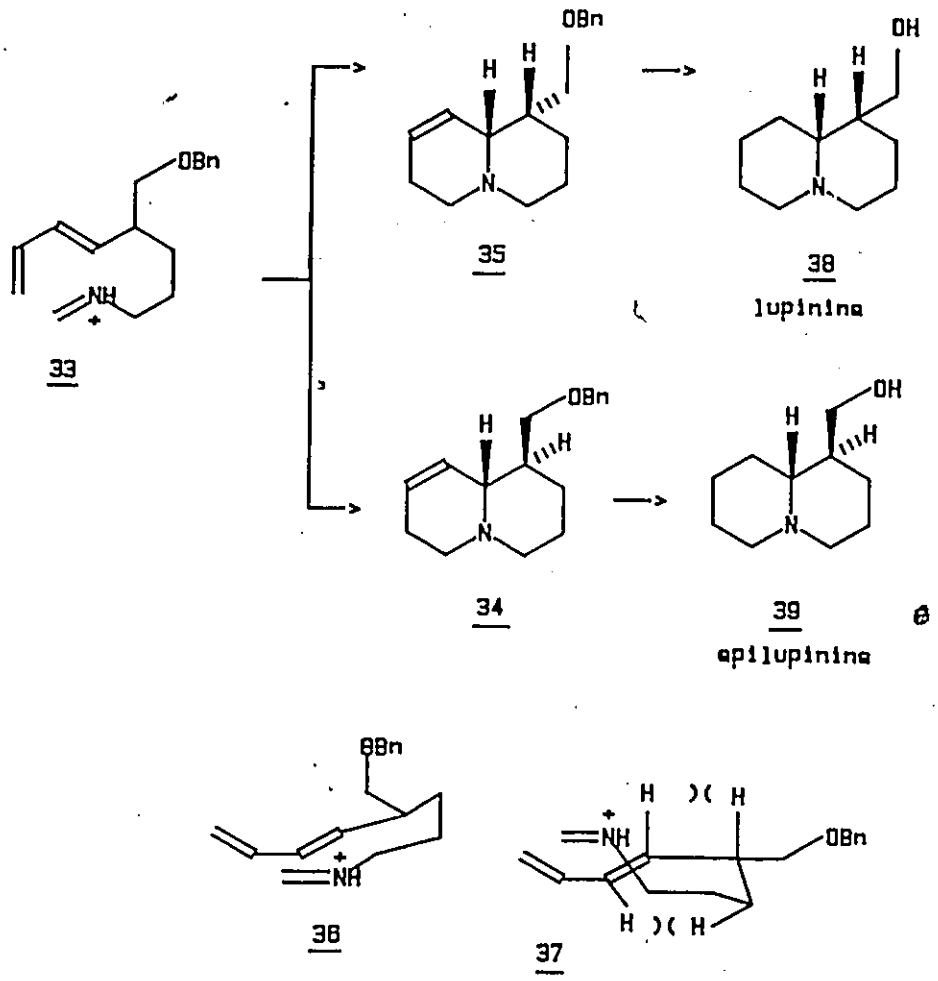


FIGURE 25. Synthesis of lupinine and epilupinine.[41]

In Weinreb's N-acylimine Diels-Alder route to 39[42] (Figure 26), wherein a boat-like transition state (41) is invoked to account for formation of a single bicyclic lactam 42 in 93% yield, none of the epimeric compound 44 was detected.

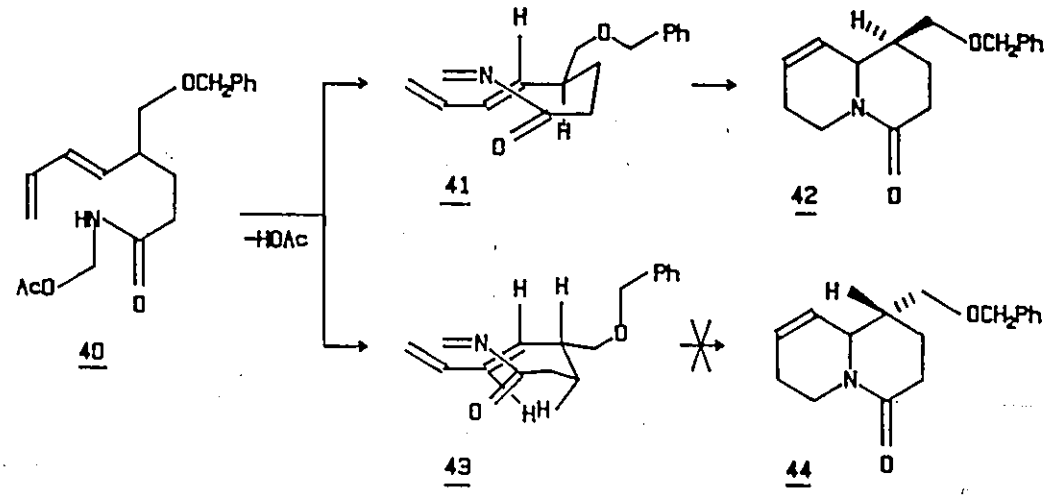


FIGURE 26. Intramolecular imino Diels Alder reaction.[42]

The N-acyl imine approach requires that in the transition state the acyl imine adopt the *s-cis endo* orientation. Therefore only two transition states, 41 and 43, are possible. Hydrogenation and reduction of 42 produces racemic epilupinine.

Takayama, *et al.*[43], described the application of the regioselective alkylation of functionalized 3-sulfolene (at the beta position) to the synthesis of the quinolizidine alkaloids, (racemic)-38 and (39). (Figure 27) Thermolysis of 45 in toluene containing $NaHCO_3$ gave lactam 47 in 80% yield *via* desulfonylation and subsequent intra-molecular Diels-Alder reaction of 46. Subsequent conversion to (racemic)-38 and

39 was accomplished *via* the aldehyde 48 after hydrogenation and reduction in 28 and 50% yield.

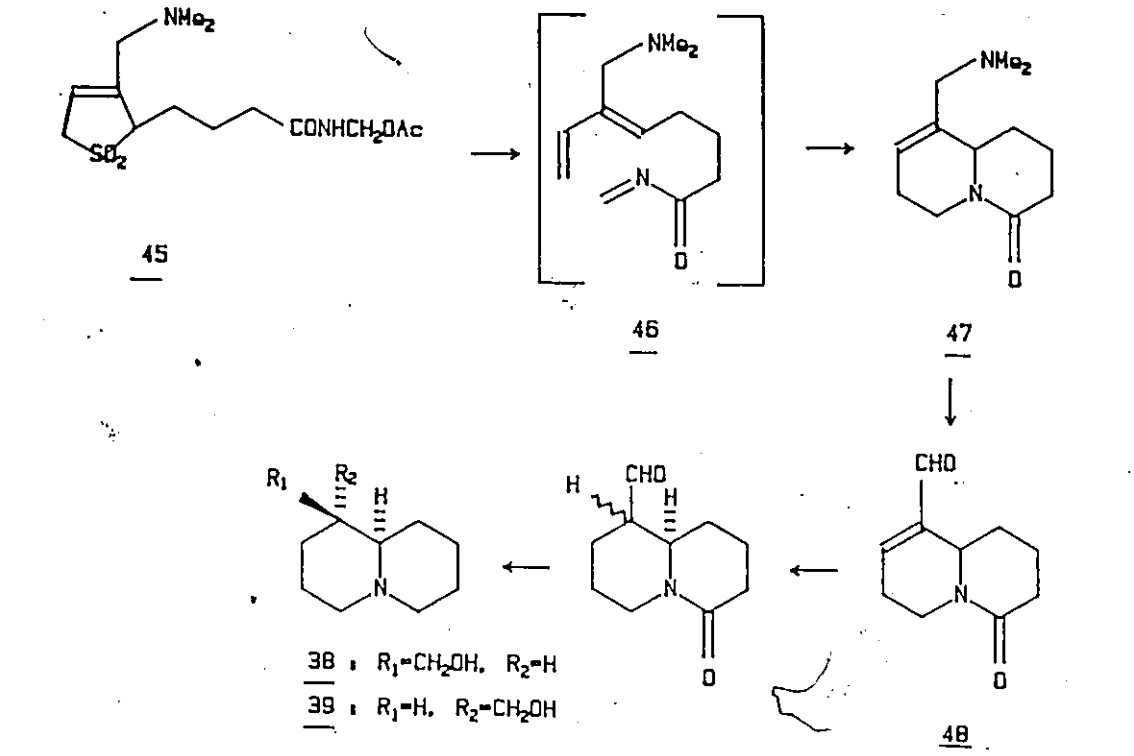


FIGURE 27. Quinolizidine synthesis via intramolecular Diels Alder reaction.[43]

Fukumoto[44] utilized an intramolecular 1-aza-1, 3-diene Diels-Alder reaction to synthesize racemic 39. (Figure 28) Heating 49 with trimethylchlorosilane, triethylamine, and zinc chloride in a sealed tube produced the quinolizidine 50 in 56% yield. Reduction produced racemic epilupinine.

Lhommet, *et al.*[45], have found that the cyclic B-enaminoester 51, undergoes intramolecular alkylation to form ethyl 1,10-dehydro lupinate 52 when heated in acetonitrile in the presence of sodium iodide. (Figure

29) Reduction utilizing Goldberg's sodium borohydride method produces racemic 53 which is further reduced to racemic lupinine.

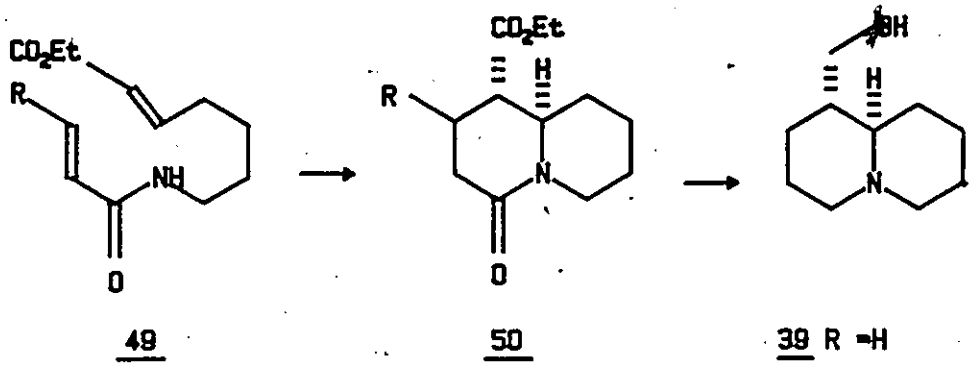


FIGURE 28. Diels Alder route to epilupinine.[44]

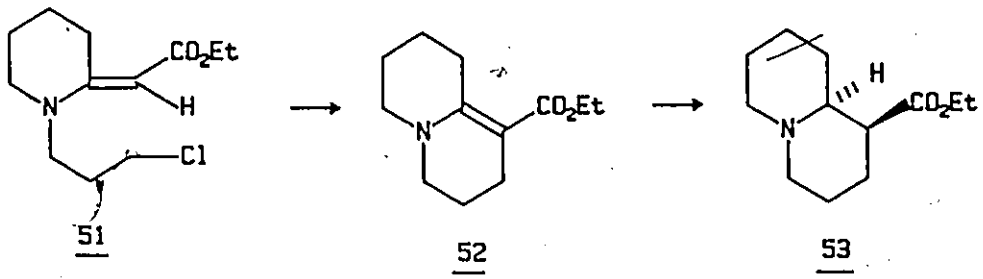


FIGURE 29. Intramolecular alkylation route to lupinine.[45]

A general synthetic route to several alkaloid ring systems utilizing cationic cyclization of ketene dithioacetals was reported by Chamberlin, *et al.*[46] (Figure 30) $NaBH_4$ reduction of imides 54a-e produced hydroxy lactam 55a-e and *in situ* mesylation and cyclization afforded 48-86% yields of the bicyclic products 56a-e.

An illustration of the synthetic utilitiy of this annulation sequence is provided by the synthesis of epilupinine. (Figure 31).

Quinolizidine 56d undergoes hydroylsis/methanolysis followed by reduction to give racemic-39 in 75% yield.

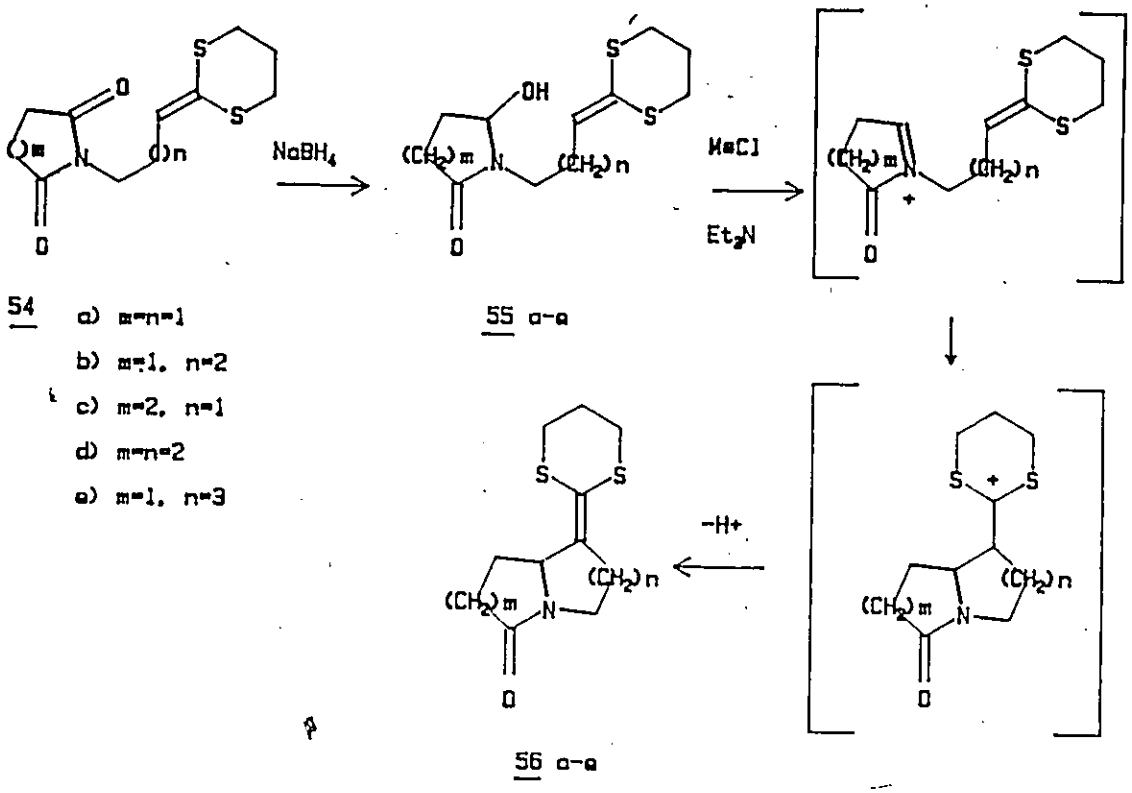


FIGURE 30. Cationic cyclization of ketene dithioacetals.[46]

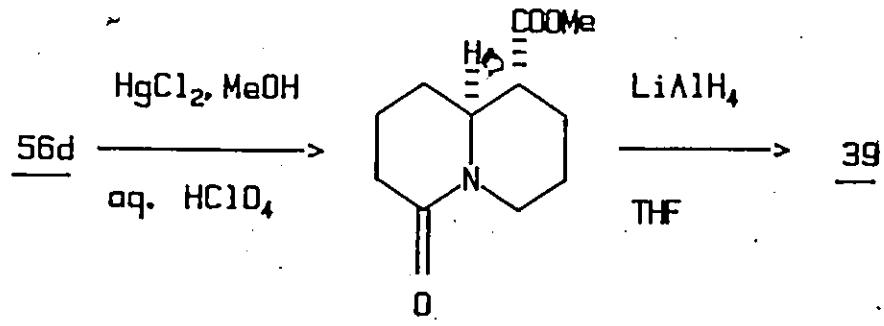
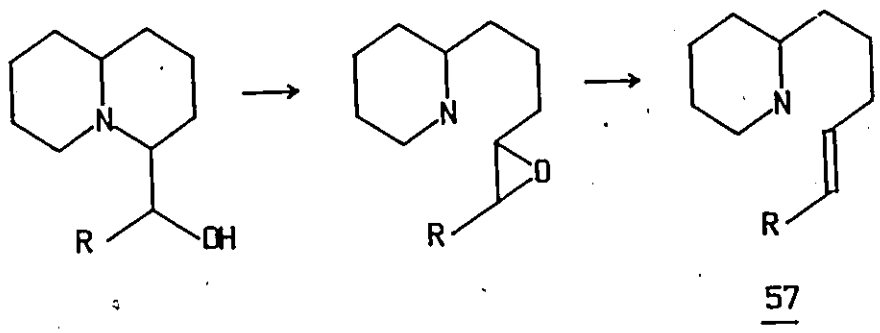


FIGURE 31. Ketene dithioacetal cationic cyclization route to epilupinine.[46]

Several novel methods for the preparation of racemic quinolizidine ring systems have been presented. We considered two approaches for the preparation of our required optically pure amino alcohols (Figure 22). A racemic synthesis could be carried out and the product resolved at some point, or an asymmetric synthesis could be attempted. In either case, the intramolecular ring opening of an epoxide[47], prepared from a common intermediate such as 57, (Figure 32) would provide a versatile route to our required amino alcohols.



57

FIGURE 32. Retrosynthesis of target molecule.

It was expected that we could prepare two stereochemically opposite epoxides starting from a common intermediate 57 (R = CH_2OH) *via* a Sharpless asymmetric epoxidation.[48] (Figure 33)

The Sharpless epoxidation provides both high yield and enantioselectivity of either epoxide enantiomer depending on which tartrate enantiomer is employed in the epoxidation of an allylic alcohol. The rules which predict which enantiomer will be obtained are illustrated in

Figure 33.[48] To date no exception to the rule governing the enantiofacial epoxidation has been reported.

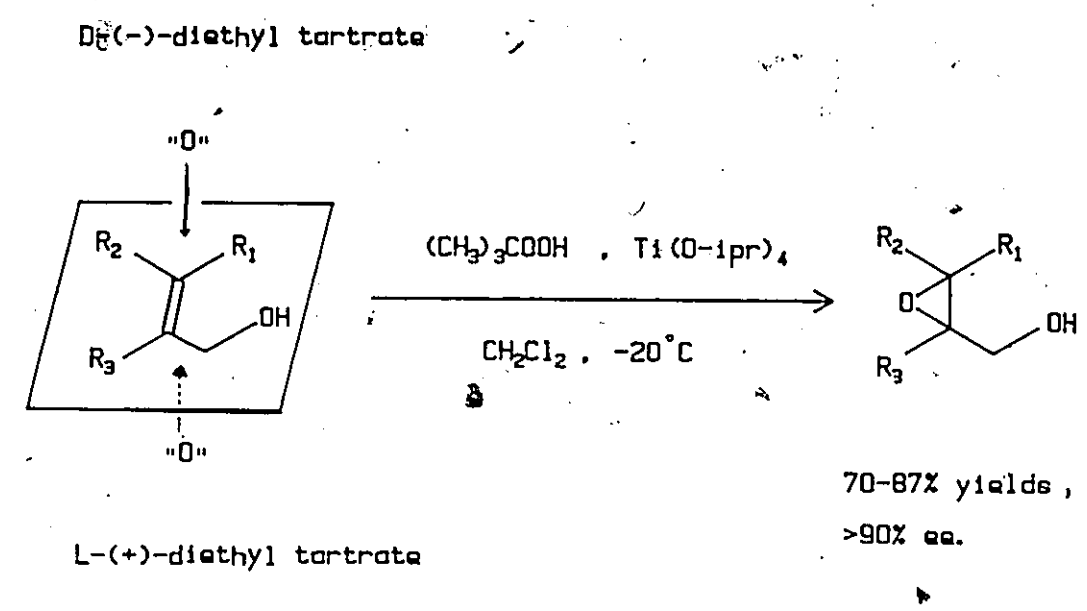


FIGURE 33. Sharpless epoxidation.[48]

Thus the stereochemical problem devolved to a synthesis of a chiral alpha-substituted piperidine such as 57. When we began our studies there were no reported methods for the direct synthesis of chiral enantiomerically pure alpha-substituted piperidines. While some reported methodologies provided moderate enantioselectivities of various alpha-substituted piperidines they were not considered suitable for our needs.[49a] On the other hand, resolution of many racemic amines has been reported.[50] Thus our first approach to the preparation of the requisite alpha substituted, enantiomerically pure piperidine (57) was to involve a racemic synthesis and resolution.

During the course of the racemic synthesis, methodologies for

stereoselective synthesis of various alpha substituted piperidines appeared in the literature.[49b,51] Of these, Husson's methodology was deemed to be most promising for the preparation of our required homochiral alpha substituted piperidine 57. Thus we decided to abandon our original racemic approach and adopt a stereoselective synthesis based on Husson's methodology. (Figure 34) This methodology involves the alkylation of 58, prepared by condensation of R-(-)-phenylglycinol and glutaraldehyde in aqueous acid with KCN. Reductive cleavage provides the chiral and enantiomerically pure alpha-substituted piperidine 59 under complete stereoelectronic control. Subsequent manipulation of the R group could then produce the required common intermediate 57. This general methodology will be described in greater detail in the results and discussion section of this thesis.

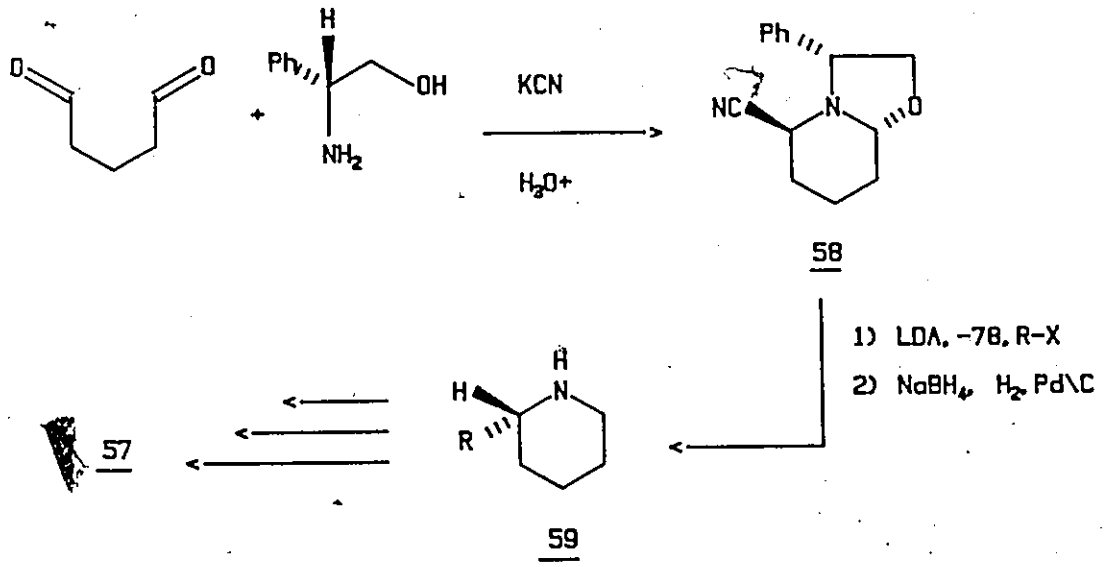


FIGURE 34. Preparation of chiral alpha-substituted piperidine.

RESULTS and DISCUSSION

Synthesis and Conformational Analysis of 4-substituted Quinolizidines

As was pointed out in the introduction, the preparation of an optically active product requires either an absolute asymmetric synthesis or resolution of the product or an intermediate leading to it. The first requirement was the preparation of a chiral alpha-substituted piperidine such as 57. The first approach involved a racemic synthesis and is outlined below. (Figure 35)

Reduction of pyridine alcohol 61, (obtained from picoline 60 via the Organic Synthesis procedure[52] in 35% yield), produced piperidine alcohol 62 in 76% yield. Acetylation of 62, (acetic anhydride, reflux, 95% yield) produced amide ester 63, which upon basic hydrolysis gave amide alcohol 64 in 65% yield. Tosylate 65 was prepared from 64 (70% yield), but the approach was abandoned at this point. Our intended route to 66 from 65 was based on methodology developed by Evans.[52a] Alkylation of 65 with 2-allylthio-2-thiazoline to give an allylic sulfide, followed by oxidation would give the sulfoxide. Thermal rearrangement of the sulfoxide would be expected to form the allylic sulfenate ester which was to be captured with a thiophile (e.g. R_3P) in a protic solvent. The product was expected to be allylic alcohol 66 (which is analogous to 57). That approach was abandoned in favor of an absolute asymmetric synthesis based on methodology developed by Husson. This approach was adopted owing to its stereoselective nature as well as its minimal number of steps.

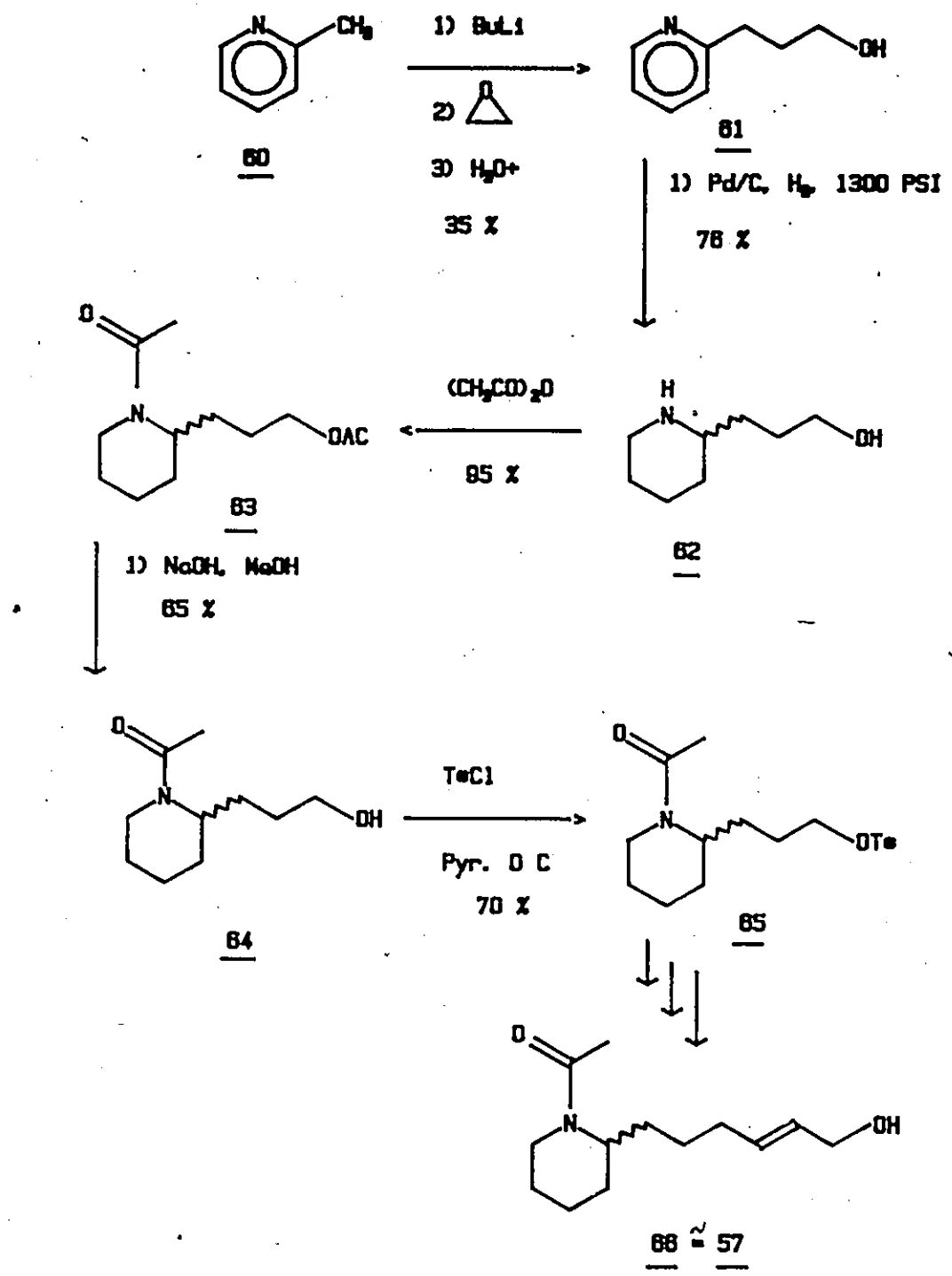
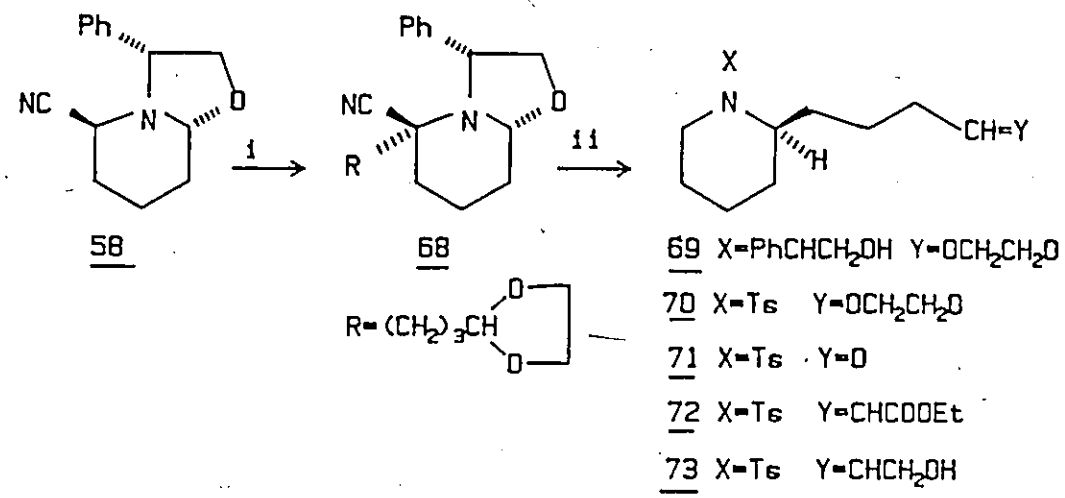


FIGURE 35. First approach to alpha-sustituted piperidine.

The preparation of the enantiomerically pure beta-amino alcohols 76a, 76b, 78a, and 78b are summarized in Figures 36, 38 and 39. Cyclization of the diastereomeric epoxides 75a and 75b (prepared as outlined in Figure 38) is outlined in Figure 39. The common intermediate (73) in the synthesis of the stereoisomeric beta-aminoalcohols was prepared as outlined in Figure 36.



i) LDA\THF\-78° 4-iodobutanal ethylene acetal (67)

ii) $NaBH_4$; H_2\Pd\C; TsCl\Et_3N; H_3O^+; $(EtO)_2P(O)COOEt$\BuLi; Dibal\THF

FIGURE 36. Synthesis of common intermediate 73.

Alkylation of the chiral oxazolidine 58[51] derived from glutaraldehyde and R-phenylglycinol[53] with 4-iodobutanal ethylene glycol acetal (67)[54] gave 68. (Figure 36) It is interesting to note that alkylation of 58 with the electrophiles indicated in Figure 37 under a variety of

conditions, could not be achieved. The failure of the chloride or

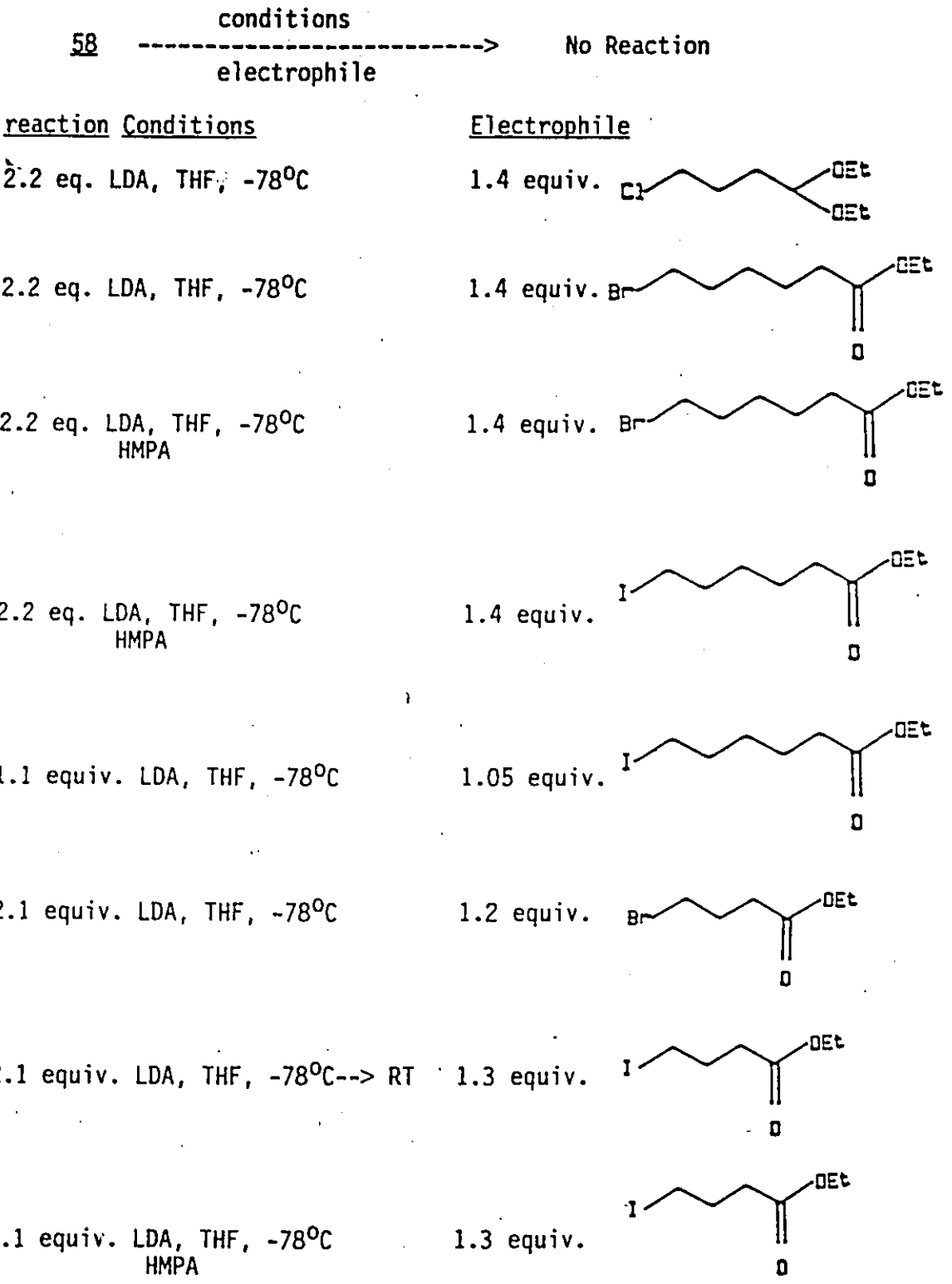


FIGURE 37. Unsuccessful alkylation reactions.

bromide to react can be attributed to their lower reactivity, but the unreactivity of the iodoesters is puzzling.

Reduction of 68 with excess sodium borohydride produced amino alcohol 69. (Figure 36) Diisobutylaluminum hydride (Dibal-H) was not effective for this transformation. Hydrogenolysis of the benzylic C-N bond (H_2, Pd/C) followed by tosylation of the nitrogen atom with toluene sulphonyl chloride and triethylamine in methylene chloride at 0°C for 3 hours followed by one half hour at room temperature gave 70 (X = Ts) mixed with the tosylate of 2-phenylethanol. Employing pyridine in place of triethylamine under otherwise identical conditions or at reflux temperatures gave only low yields (10 - 30%) of 70. The mixture of tosylates could be separated using column chromatography. Hydrolysis of the unseparated mixture of 70 and the tosylate of 2-phenylethanol followed by chromatographic purification produced aldehyde 71 in 74% overall yield from 69. The diastereomeric purity of 69, and thus the enantiomeric purity of 70 and 71, was established by proton and carbon NMR experiments. The amino alcohol 69 showed no extra peaks in the 75MHz ^{13}C and 300MHz ^{1}H NMR spectra suggesting that a single diastereomer was present. (Figure 37a) This implies reductive decyanation at C_2 is 100% stereoselective. This stereoselectivity involves an elimination - addition mechanism wherein hydride ion approaches a preferred iminium conformer (formed by elimination of the cyano group) under complete stereoelectronic control from the axial direction.[51,55] (Figure 37b) In other words, attack of the hydride ion on the upper face of the conformationally rigid iminium ion, trans and diaxial to the developing lone pair of electrons on the nitrogen atom leads to the chair-like intermediate shown whereas addition to the lower face in the same manner leads

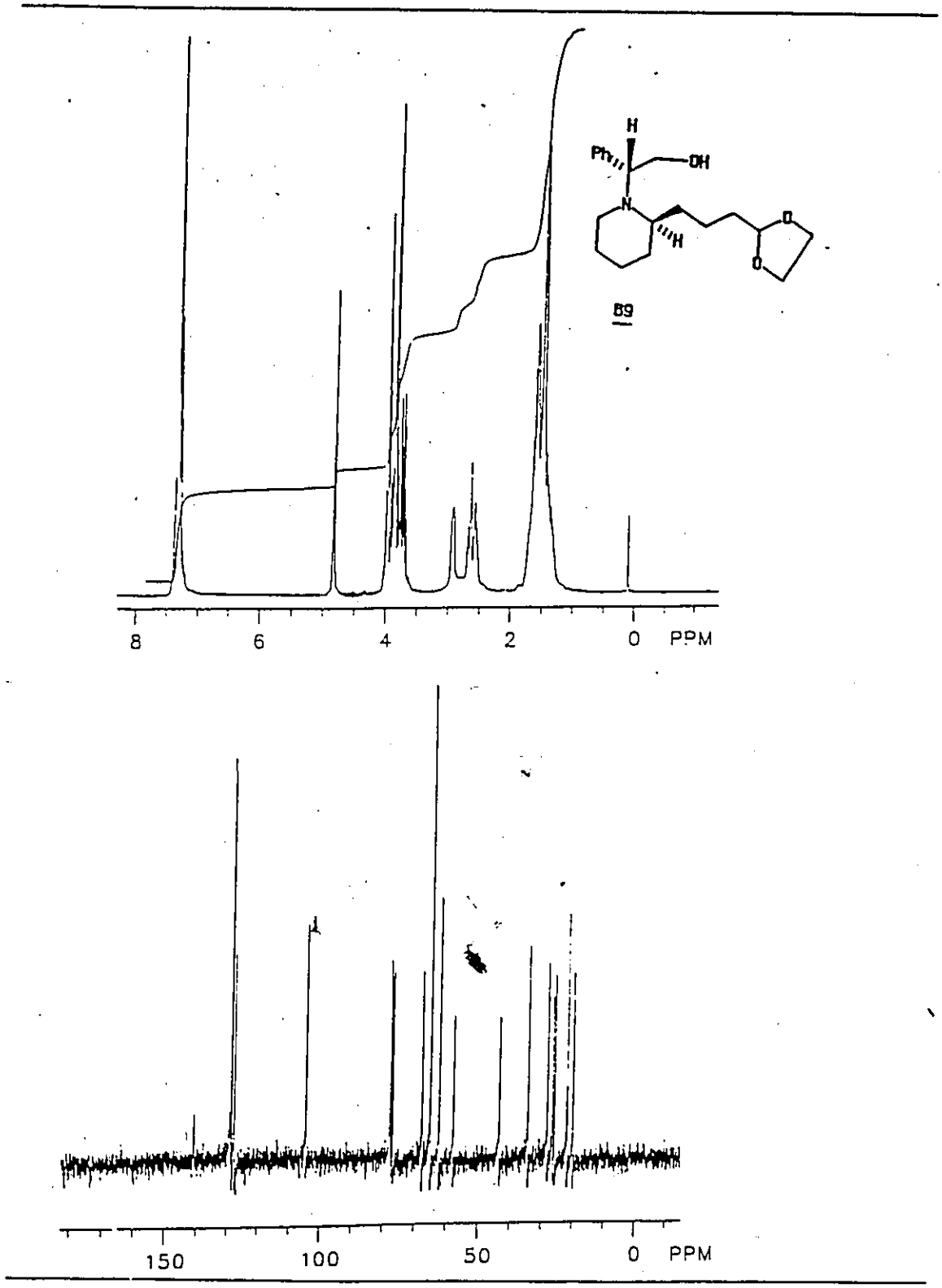


FIGURE 37a. Proton and ^{13}C NMR spectra of 69.

to a boat-like intermediate. The chair-like product is obtained since the transition state leading to it is more favorable than that leading to the boat-like intermediate. (Figure 37b) After hydrogenolysis of the chiral appendage of 69 the remaining chiral center of 70 and 71 is assigned the R configuration in analogy with Husson's work. Chain homologation using the Horner-Emmons modification of the Wittig reaction[56] provided the conjugated ester 72. The double bond configuration in 72 is expected[56] to be E and this was supported by the proton and carbon NMR spectra which showed no indication of any other stereoisomers.

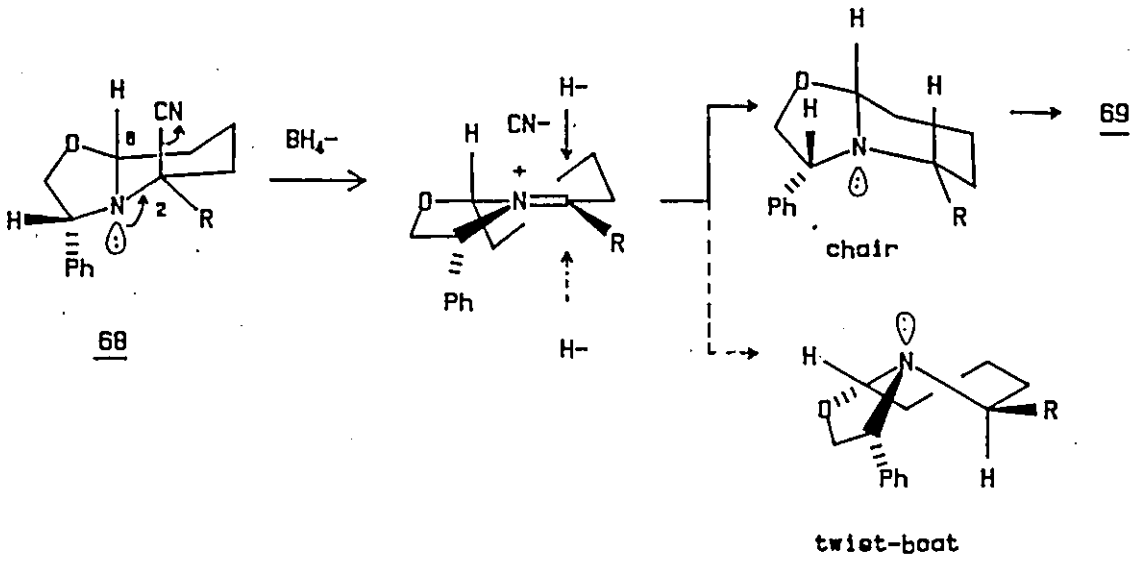


FIGURE 37b. Stereoelectronically controlled hydride reduction of 68.

Examination of the ^1H NMR spectrum revealed that two doublets of triplets were present for the two vinylic protons as expected (δ = 6.93, 5.81). (Figure 37c) The major coupling constant (J = 15.7 Hz) is indica-

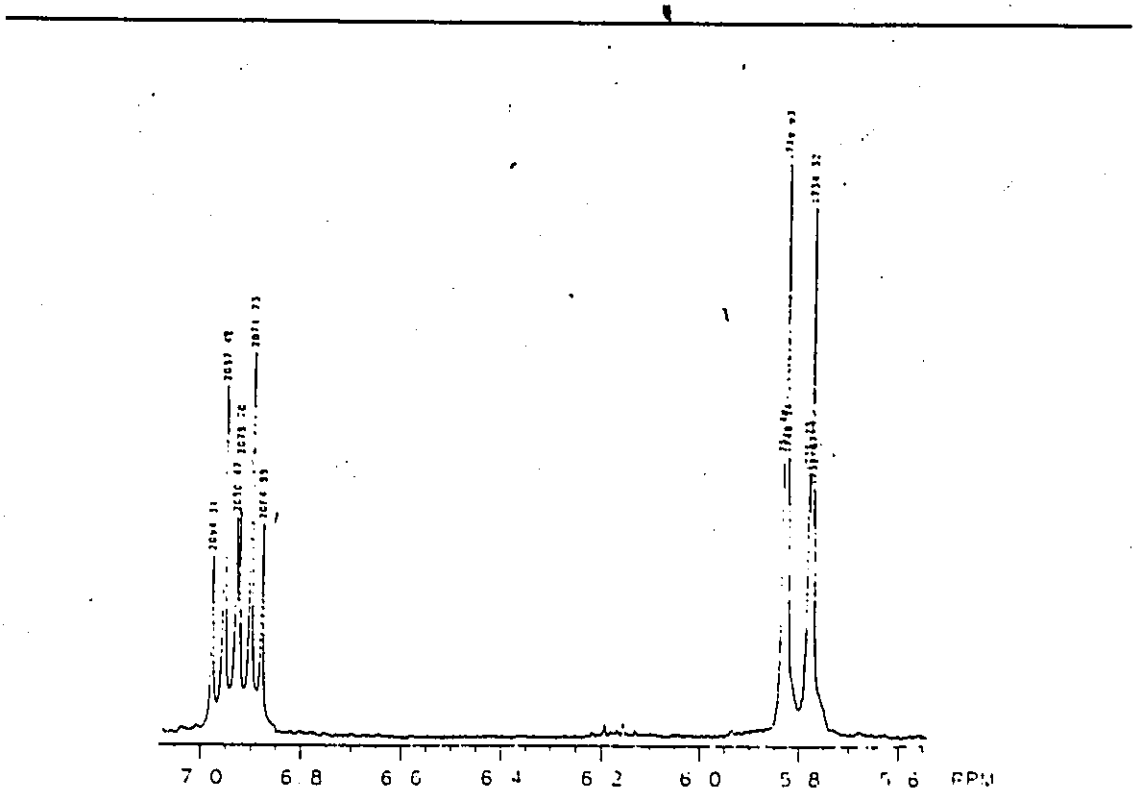
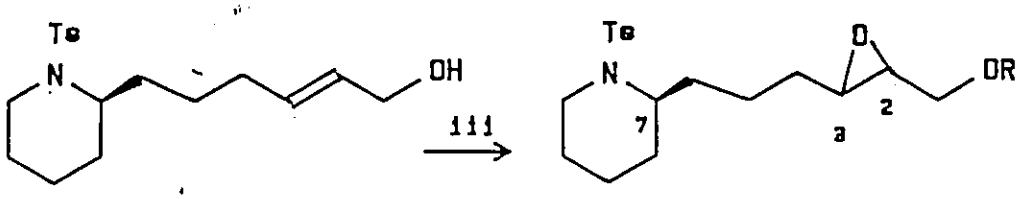


FIGURE 37c. ^{1}H NMR spectrum of vinylic protons of 72.

tive of a trans arrangement of these protons on the double bond. A cis arrangement would have given J = 2-10 Hz. Reduction of 72 with DIBAL gave alcohol 73, the common intermediate in the synthesis of the two stereoisomers. (Figure 36) The overall yield of 73 from 58 was 41%.

Transformation of the planar E-configuration of 73 into the tetrahedral asymmetry of 74 was achieved by Sharpless epoxidation[48] with (+)-Diethyl tartrate ((+)-DET) or (-)-Diethyl tartrate ((-)-DET). (Figure 38) As outlined in the introduction, either diastereomer of epoxide 74 can be formed in excess from allylic alcohol 73 depending on which tartrate enantiomer is employed. Sharpless epoxidation with (+)-DET gave epoxide 74a as the major diastereomer contaminated with 74b

whereas epoxide 74b was obtained as the major diastereomer when (-)-DET was employed. The contaminant in this case was 74a. The products of the two epoxidation reactions were physically different. The mixture containing 74a in excess was an oil whereas that containing 74b was a



73

74 R=H 75 R=Bn

a C_2-S, C_3-S, C_7-R 92% de

b C_2-R, C_3-R, C_7-R 91% de

iii) $Ti(O\text{-}iPr)_4$, (+)-DET or (-)-DET, t-BuOOH; NaH, THF, $PhCH_2Br$

FIGURE 38. Preparation of diastereomeric epoxides 75a and 75b.

crystalline solid. Using the rule[48] described in the introduction section of this dissertation which was developed for prediction of the stereochemistry of the major products of Sharpless epoxidations, 74a can be assigned the 2S,3S,7R configuration and 74b the 2R,3R,7R configuration. The two diastereomers present in each epoxidation mixture exhibited identical Rf values and thus they could not be separated. Their ^1H NMR spectra were indistinguishable. The ^{13}C NMR spectrum of the mixture containing epoxide 74a in excess showed a small signal (δ= 52.5) for one carbon (C-10) which correlated with the major C-10 absorption for the mixture which contained compound 74b in excess and the reverse was also true. (Figure 38a) However, the diastereomeric excess calculation

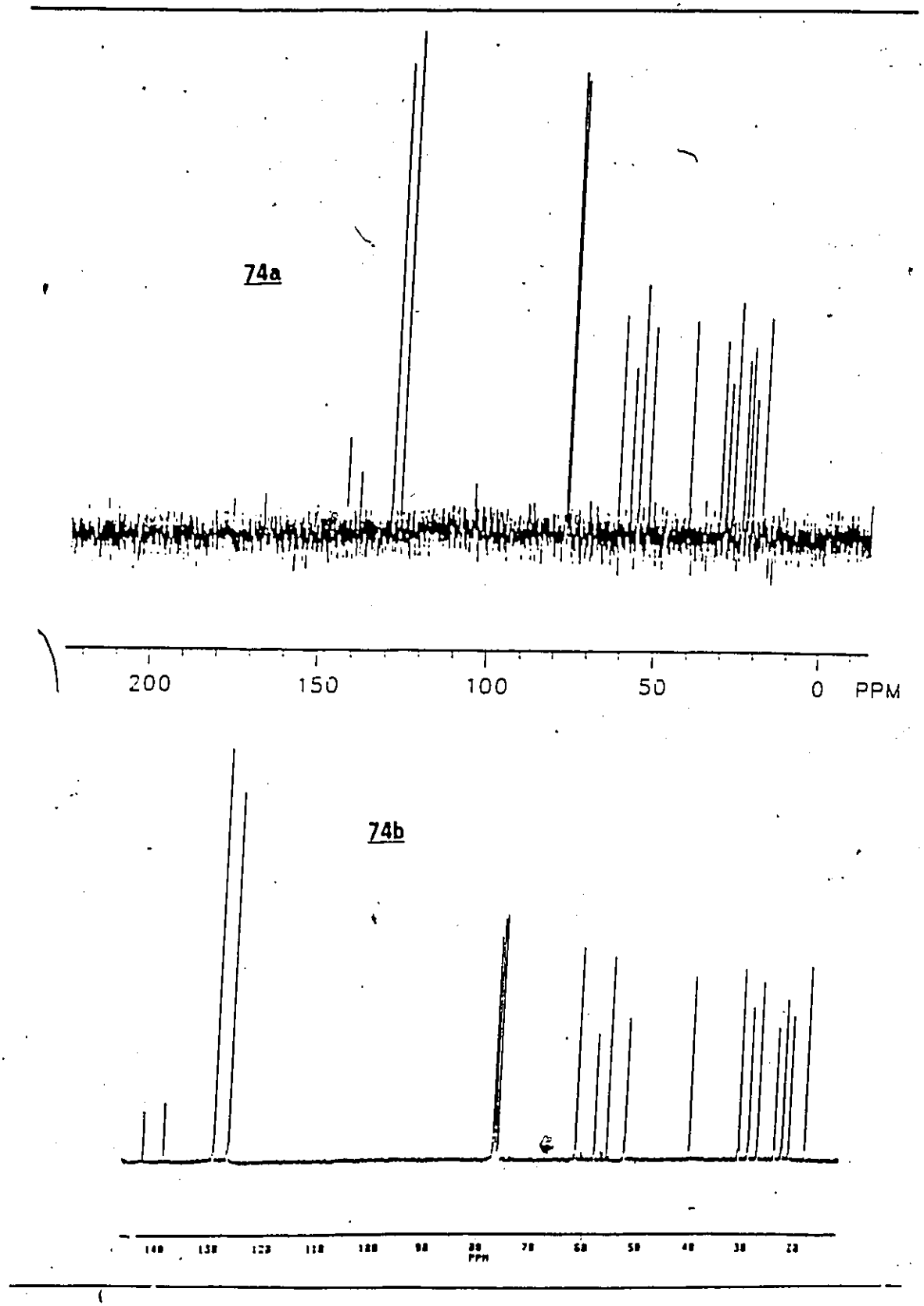


FIGURE 38a. ^{13}C NMR spectra of 74a and 74b

made on this basis deviated very significantly from that made on the basis of the ^1H NMR of the corresponding Mosher ester. This is most likely due to a difference in relaxation times of the C-10 carbons for the two diastereomers 74a and 74b. The ^{19}F NMR of the (+)-MPTA derivatives[57] showed signals which were overlapping (δ = 8.82), but based on their ^1H NMR spectra, and using the absorptions for the C-1 protons, diastereomeric excesses for 74a and 74b of approximately 92% and 91% could be determined. Some signal overlap still exists in these spectra and the de's quoted above represent worst case scenarios. Therefore the mixture containing 74a in excess (Figure 38) is contaminated by 4% of 74b and the mixture containing 74b contains 4.5% of 74a. The same must be true for the prepared benzyl epoxides 75a and 75b. Benzylation of alcohols 74a and 74b employing benzyl bromide and sodium hydride in THF provided 75a and 75b respectively which again show essentially identical Rf and ^1H NMR spectra. The ^{13}C NMR of 75a and 75b were similar in form to those described above for the epoxy alcohols 74a and 74b. The spectrum of the mixture containing 75a in excess showed a small signal (δ=52.6) for C-10 which correlated with the major C-10 absorption for the mixture which contained 75b in excess and the reverse was also true.

Cyclization of the epoxides 75 to quinolizidines 76 was effected by treatment with two equivalents of sodium naphthalenide in DME at -60°C.[58] (Figure 39)

At this point in the synthesis, a distinct difference between the stereoisomers was observed. Epoxide 75b (which contained 4% of 75a) afforded a single crystalline amino alcohol (76b) in 70% yield, whereas 75a (which contained 4.5% of 75b) gave two isomeric products plus traces of other compounds. The major product from 75a (35%) is assigned struc-

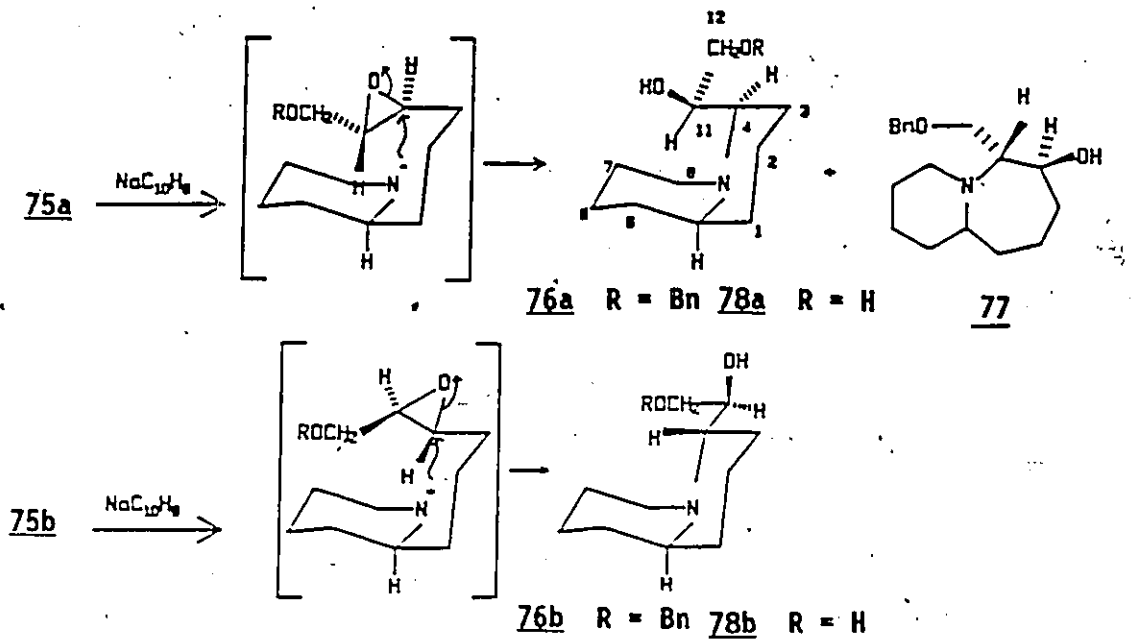


FIGURE 39. Cyclization reaction.

ture 76a on the basis of its spectroscopic properties as detailed below. The structure of the other isomer (4%) remains in doubt at this time although 77 cannot be ruled out. The chromatographic mobilities of 76a and 76b were quite different and it was possible to obtain these materials diastereomerically pure and without cross contamination. Because alcohol 73 was enantiomerically pure, it follows that pure enantiomers of 76a and 76b were in hand.

Valuable information was obtained from the proton NMR spectra of 76a and 76b. (Figure 40) The formation of the six-membered ring was indicated by proton NMR decoupling experiments. In each case, the two doublets of doublets ($\mathcal{J}$ = 3.5) due to

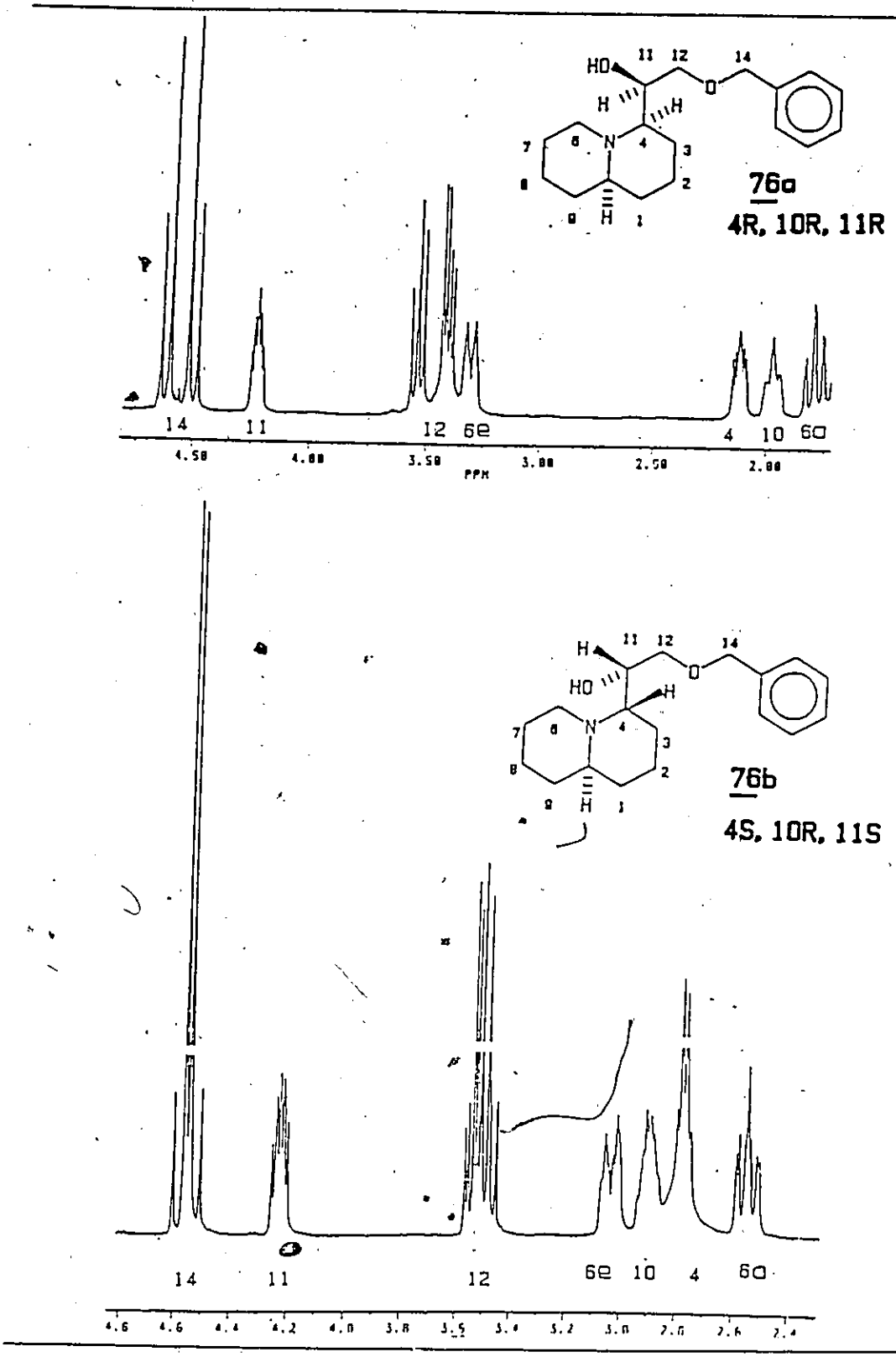


FIGURE 40. ^{1}H NMR spectra of quinolizidines 76a and 76b.

the C-12 protons were coupled to only one other proton whose chemical shift (δ=4.23 for 76a and 4.24 for 76b) was indicative of an oxygenated carbon. This proton was further coupled to only one other proton (δ=2.14 in 76a and 2.78 in 76b). The coupling pattern would be quite different if the alternative seven-membered ring closure product 77 had been obtained. DEPT (distortionless-enhancement-by-polarization-transfer)[59] (Figure 40a) editing of the ^{13}C NMR spectra allowed identification of the methine resonances and subsequent single frequency proton decoupled carbon spectra and C-H correlated 2D allowed the assignment of the the protons in the ^{1}H spectrum which were attached to the methine carbons. Since the protons attached to C-4 and C-11 had previously been identified, the remaining methine proton must be attached to C-10. This information was necessary for the conformational analysis of these systems *(vide infra)*.

The differences in cyclization efficiency of 75a and 75b can be nicely rationalized on the basis of steric effects. (Figure 39) Assuming that epoxide opening occurs from an all chair transition state, with inversion of configuration and axially with respect to the nitrogen-containing ring[60], it can be seen that the epoxide and its associated benzyloxy group must lie directly over the piperidine ring in 75a. A severe steric interaction results destabilizing the transition state leading to 76a and lowering its yield. However, in 75b, the epoxide and its associated benzylozy group is rotated away from the ring and it is the hydrogen which resides over the ring. The transition state leading to 76b is less crowded than that leading to 76a and a higher yield of 76b is obtained. Using the same assumptions, the configuration of 76a

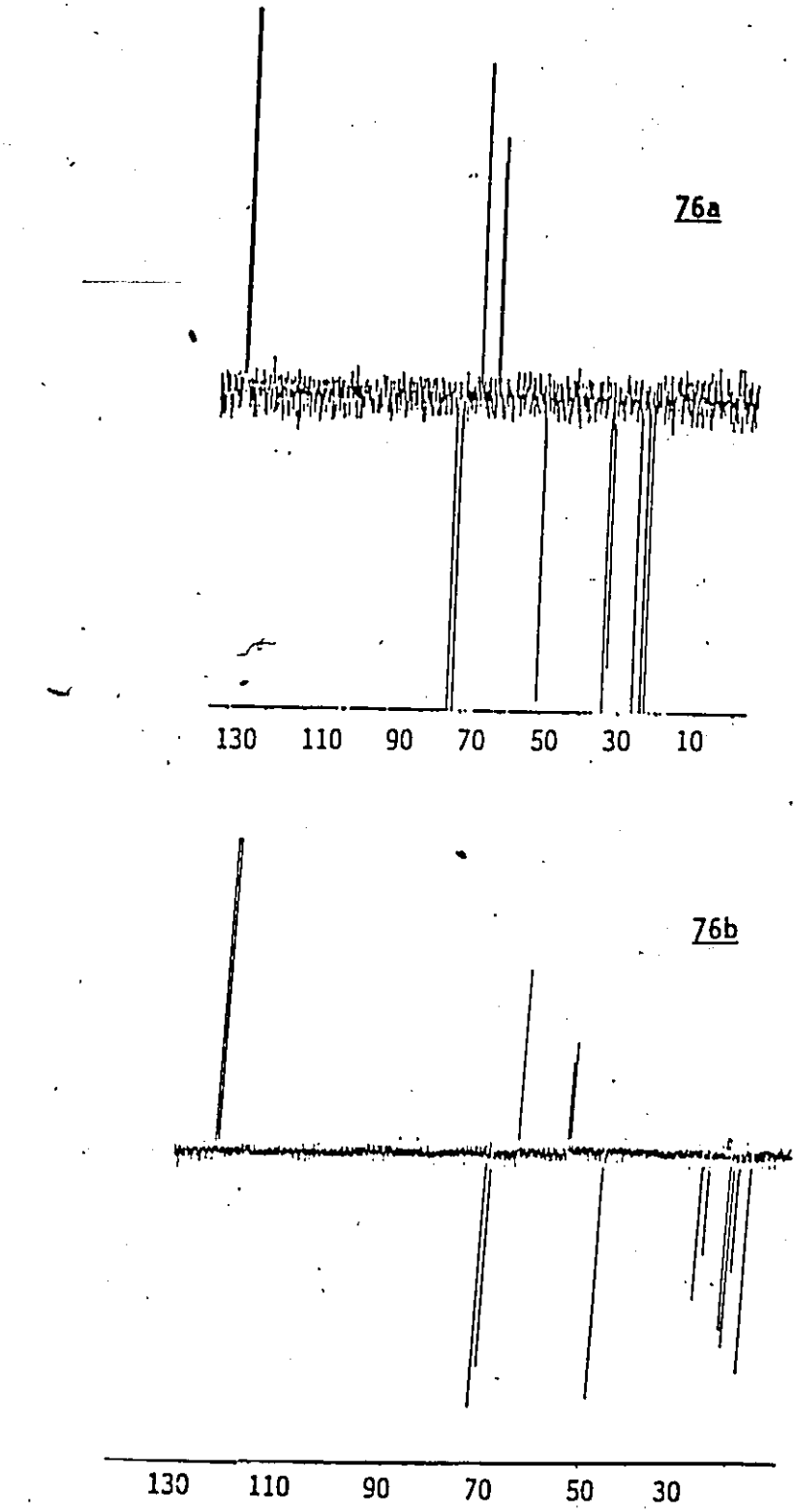
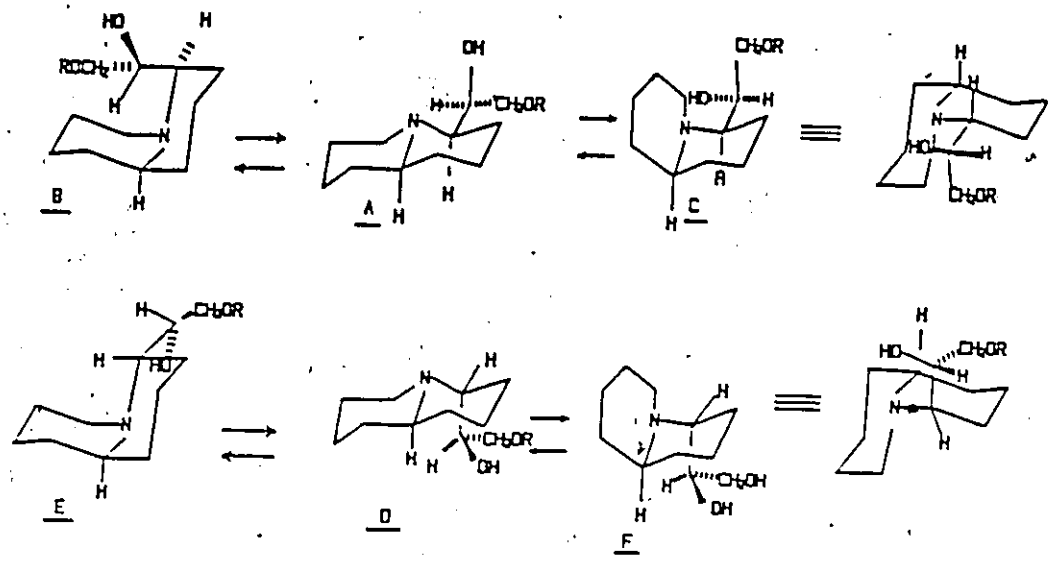


FIGURE 40a. ^{13}C DEPT NMR spectra of 76a and 76b.

can be designated (using the quinolizidine numbering system) as 4R,10R,11R and that of 76b must be 4S,10R,11S. (Note that the priorities of the substituents on C-11 change during the cyclization leading to a reversal of its stereochemical descriptor). Catalytic hydrogenolysis of 76a and 76b gave diols 78a (27% from 73, 11.1% from 58, 10 steps) and 78b respectively (50% from 73, 21% from 58, 10 steps). These diols were found to be water soluble.

In order to meaningfully interpret stereochemical data from reactions using 76a,b or 78a,b as catalysts, their preferred solution conformations must be known. Of course the argument that the solution conformation bears no necessary resemblence to the composition of the catalytically active species is valid. Complexation with metals and salt formation are very strong forces which may easily outweigh conformational effects. However, in the absence of any other structural data on the conformation of the catalytically active species, the solution conformations of 76a,b and 78a,b are all we have to go on. The possibility of nitrogen-inversion is a complicating factor which allows conversion of a cis-fused quinolizidine system into a trans-fused one.

As outlined in the introduction section of this dissertation, conformational analysis of the quinolizidine ring system is aided by the presence of the nitrogen atom. As a result of nitrogen inversion, three all-chair conformations are possible for each of 76a and 76b. (Figure 41) Conformations A, B and C can accommodate the substituted quinolizidine ring 76a (4R, 10R, 11R). The *trans*-fused quinolizidine conformer A possesses a C-4 equatorially disposed substituent. The two *cis*-fused conformers B, and C result from inversion at nitrogen leaving the C-4 substituent axially and equatorially disposed respectively. Intramolec-



R = CH_2Ph

FIGURE 41. Possible conformmations of 76a and 76b.

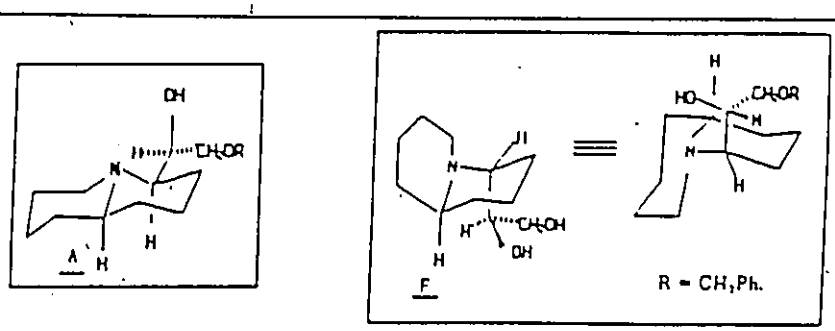
ular hydrogen-bonding is possible in conformers A and C but not in B. Similarly, the C-4 substituted quinolizidine 76b (4S, 10R, 11S) can be accommodated by three all-chair conformations D, E and F. (Figure 41) In this case, the *trans*-fused conformer D possesses an axially disposed C-4 substituent and does not allow the possibility of intramolecular hydrogen bonding. Cis-fused conformers E and F possess C-4 substituents which are equatorially and axially disposed respectively which do allow for possible intramolecular hydrogen bonding. Hydrogen bonding has been shown to be an important factor in determining preferred conformations of substituted quinolizidines. For example, it is known that the solution conformation of lupinine (*trans*-fused ring) 38 is such that the hydroxymethyl substituent is axial so as to allow intramolecular hydrogen bonding.[61]

Our conclusions regarding the preferred conformations of 76a and 76b rest primarily on their ^{1}H NMR spectra. The ^{1}H and ^{13}C NMR spectra of variously substituted quinolizidines have been the subject of many investigations[37] and conformational effects, particularly in the proton spectra, seem well defined. The results can be summarized as follows: protons immediately adjacent to nitrogen show characteristic chemical shifts which depend on the dihedral angle between the proton and the nitrogen lone pair of electrons. An antiperiplanar arrangement causes a significant upfield shift (typical value = 2 ppm) relative to protons which have dihedral angles of 60^{o} or 120^{o} (typical value = 3 ppm) ($\Delta\delta$ = 0.8 - 1 ppm). The dihedral angles of the protons on the three conformations of each of 76a and 76b are shown in Table 3 along with the expected and observed chemical shifts.

TABLE 3. Observed and expected chemical shifts for conformations of 76a, 76b, 78a and 78b.

Conformation	dihedral angles with N lone pair				δ for C4, C6e, C6a, C10	
	C4	C6e	C6a	C10	expected	observed
A	180	60	180	180	2, 3, 2, 2	2.12, 3.30, 1.79, 1.97 (76a)
						2.09, 3.34, 1.97, 1.80 (78a)
B	60	60	60	60	3, 3, 3, 3	
C	60	60	180	60	3, 3, 2, 3	
D	60	60	180	180	3, 3, 2, 2	
E	180	60	60	60	2, 3, 3, 3	
F	60	60	180	60	3, 3, 2, 3	2.80, 3.05, 2.55, 2.91 (76b)
						2.73, 3.13, 2.58, 3.13 (78b)

The specific protons were identified by the decoupling experiments previously described. As can be seen, the observed chemical shifts for 76a and 76b correlate with the expected shifts for conformers A and F respectively as the predominant forms. In an analogous manner diols 78a and 78b are assigned conformer A and F (R = H), respectively. (Figure 42 and Table 3) The possibility that the phenyl ring present in 76a and 76b might be affecting the observed chemical shifts of the protons adjacent to the nitrogen atom was eliminated when the phenyl group was removed giving the diols 78a and 78b which exhibited chemical shifts consistent with those seen for 76a and 76b.



76a = conformation A

76b = conformation F

FIGURE 42. Preferred Conformations of 76a and 76b

Quaternization of the amino alcohols 76a, 76b, 78a and 78b would provide access to a group of stereochemically interesting chiral ammonium salts with the potential to be effective phase transfer catalysts. To this end we refluxed 76b with excess benzyl bromide in a variety of solvents (ether, ethanol, acetonitrile, toluene). Unfortunately we were not able to isolate any of the desired quaternary ammonium salt. Increasing the temperature beyond 110°C was not considered practical since as the temperature increased, decomposition of the starting material occurred. Although quaternization of 76b with methyl iodide would be

expected to proceed more readily than with benzyl bromide, it would provide a quaternary ammonium salt which would not possess the specific pi-pi overlap required for high enantioselectivity (see Introduction) and thus was not examined.

As the foregoing outlines, we have prepared two enantiomerically pure diastereomers of each of two substituted quinolizidine system[61b] whose functionality makes them potentially useful for catalytic purposes. Such application of these materials is the subject of the next section of this thesis.

Catalytic Study

At this point, it is important to recall our working definition of the word "catalyst" which was presented in the introduction (p.1)

Our original plan was to quaternize the chiral amino alcohols 76a, 76b, 78a and 78b and use the salts as chiral phase transfer catalysts. However all attempts to obtain the benzylated salt of 76b were unsuccessful. Since we could not study the PTC reaction we turned our investigation to another reaction reported to be catalyzed by beta-amino alcohols.

Metal salts of chiral beta-amino alcohols have been reported to catalyze alkylzinc addition to aldehydes to give secondary alcohols with varying degrees of enantioselectivity. (Figure 9)[15-22] Application of the metal salts of the diastereomeric 4-substituted quinolizidines 76a/76b and 78a/78b (Figure 39) as catalysts for this reaction was investigated. The diethylzinc addition to benzaldehyde in the presence of five mol percent of the quinolizidine catalyst was the specific reaction investigated. (Figure 43)

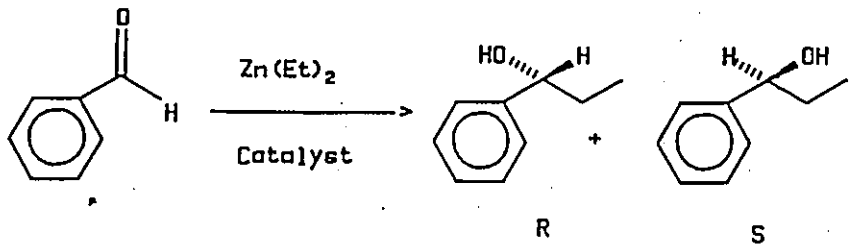


FIGURE 43. Diethylzinc addition to benzaldehyde.

As outlined in the introduction this reaction is attractive as it is experimentally simple to perform, the products are easily isolated and the enantioselectivity can be determined by reference to literature rotation values and is easily checked by the NMR spectra of the MTPA-esters. (Figure 44)

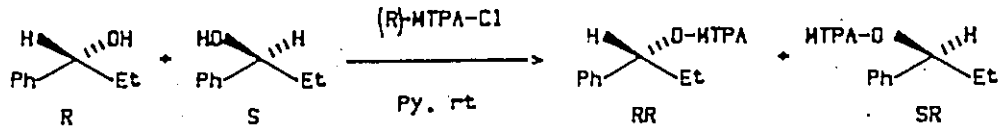


FIGURE 44. Preparation of Mosher esters.

Compounds 76a and 76b were each tested under two conditions; i) as their Lithium alkoxides and ii) as their Zinc alkoxides; whereas compounds 78a and 78b were tested as their Zinc alkoxides only. The lithium salt of the amino alcohols tested were prepared by adding one equivalent of BuLi to a solution of the amino alcohol in toluene and stirring 15 minutes at 0^{o} C prior to adding the benzaldehyde and diethylzinc. The reaction was allowed to warm from 0^{o}C to ambient temperature 2 hours after the addition of the aldehyde and diethylzinc. The progress of the

reaction was monitored by gas chromatography. The zinc salt was prepared by adding one equivalent of diethylzinc to a toluene solution containing the amino alcohol and refluxing for 30 minutes. After cooling to 0^{o} C, the aldehyde and diethylzinc were added and the reaction was allowed to proceed as outlined above for the lithium salt. The reaction conditions were chosen to duplicate literature precedents in order to allow direct comparisons to be made. The quinolizidines were recovered in essentially quantitative yield. The results are reported in Table 4.

When the lithium alkoxide of 76a was employed as the catalyst with benzaldehyde and diethylzinc the reaction gave a 98% yield of (S)-1-phenyl-1-propanol in 84.1% enantiomeric excess accompanied by 1% unreacted benzaldehyde and 1% benzyl alcohol after stirring 23 hours at ambient temperature (entry 1, Table 4). The desired alcohol, 1-phenyl-1-propanol was separated from the benzaldehyde and benzyl alcohol by silica gel chromatography. The predominant enantiomer was assigned the S configuration by comparison of the sign of optical rotation with literature data. The rotation was negative, -37.9^{o} (c = 5.15, $CHCl_3$), which correlates with the literature value (-45.5^{o}, c=5.15, $CHCl_3$) for the S enantiomer.[57]

In contrast the lithium alkoxide of 76b produced the R enantiomer of 1-phenyl-1-propanol in 38% enantiomeric excess and in 85% chemical yield together with 3% unreacted benzaldehyde and 12% of benzyl alcohol after 18 days at room temperature (entry 2). The predominant alcohol enantiomer formed was assigned the R configuration upon analysis of the ^{1}H NMR spectrum of the corresponding Mosher esters. (Figure 45) The peaks for the major Mosher diastereomer of the products derived employ-

TABLE 4

Addition of Diethylzinc to Benzaldehyde using chiral 4-substituted Quinolizidines as Catalysts[a].

Entry	time(h)	catalyst	yield[b] GC	yield[b] isolated	deg[c]	enantiomeric excess[d]	config.[e]
1	23	76a[f]	98	81	-37.9 (5.15,$CHCl_3$)	84	S
2	432	76b[f]	85	60	-	38	R
3	80	76a[g]	72	52	-	32	S
4	80	76b[g]	70	51	-	28	R
5	120	78a[g]	75	59	-	55	S
6	120	78b[g]	76	62	-	58	R

(a) aldehyde: diethylzinc: catalyst mol. ratio , 1.0: 1.2: .05 in toluene as solvent

(b) Isolated yields not based on unrecovered benzaldehyde.

(c) Lit. value (S)-1-phenyl-1-propanol, $[\alpha]_D$= -45.45, (c =5.15,$CHCl_3$)

(d) Determined by ^1H and ^{19}F analysis of Mosher esters.

(e) Determined by comparison of known absolute rotation with experimental value obtained.

(f) 1 equiv. BuLi added (based on amino alcohol).

(g) 1 equiv. $ZnEt_2$ added (based on amino alcohol).

(h) h = hours

ing 76b as a catalyst were opposite to those derived employing 76a which was assigned the S configuration. A similar trend was observed upon examination of the two peaks of the corresponding ^{19}F NMR spectra (δ=6.18, 6.44). (Figure 46)

When the zinc alkoxide of 76a was utilized, a 72 % conversion of benzaldehyde produced the S isomer of 1-phenyl-1-propanol in 32% enantiomeric excess accompanied by 24% unreacted benzaldehyde and 4% benzyl alcohol after 80 hours at ambient temperature (entry 3). Similarly 76b gave 70% conversion of benzaldehyde producing the R isomer along with 20% of benzaldehyde and 10% of benzyl alcohol after 80 hours at room temperature (entry 4).

When the zinc alkoxide of diol 78a was employed as the catalyst a 75% yield of the the S enantiomer in 55% enantiomeric excess was obtained after 120 hours accompanied by 23% of recovered benzaldehyde and 2% of benzyl alcohol (entry 5). The zinc alkoxide of a diol 78b produced a 76% yield of the R enantiomer in 58% enantiomeric excess after 120 hours accompanied by 20% of unreacted benzaldehyde and 4% of benzyl alcohol (entry 6).

In general, under the reaction conditions tested, it was observed that 76a and 78a produced the S enantiomer of 1-phenyl-1-propanol in excess whereas 76b and 78b produced the R enantiomer in excess. Therefore, although the quinolizidines tested were diastereomeric they functioned as enantiomers. This result is not surprising since a close examination of the catalysts 76a/76b and 78a/78b reveals that while they do represent diastereomeric pairs, the catalytic sites - the B-hydroxy amine portions of the molecules - are enantiomeric. (See Abstract) Therefore 76a would be expected to produce one enantiomer in excess and

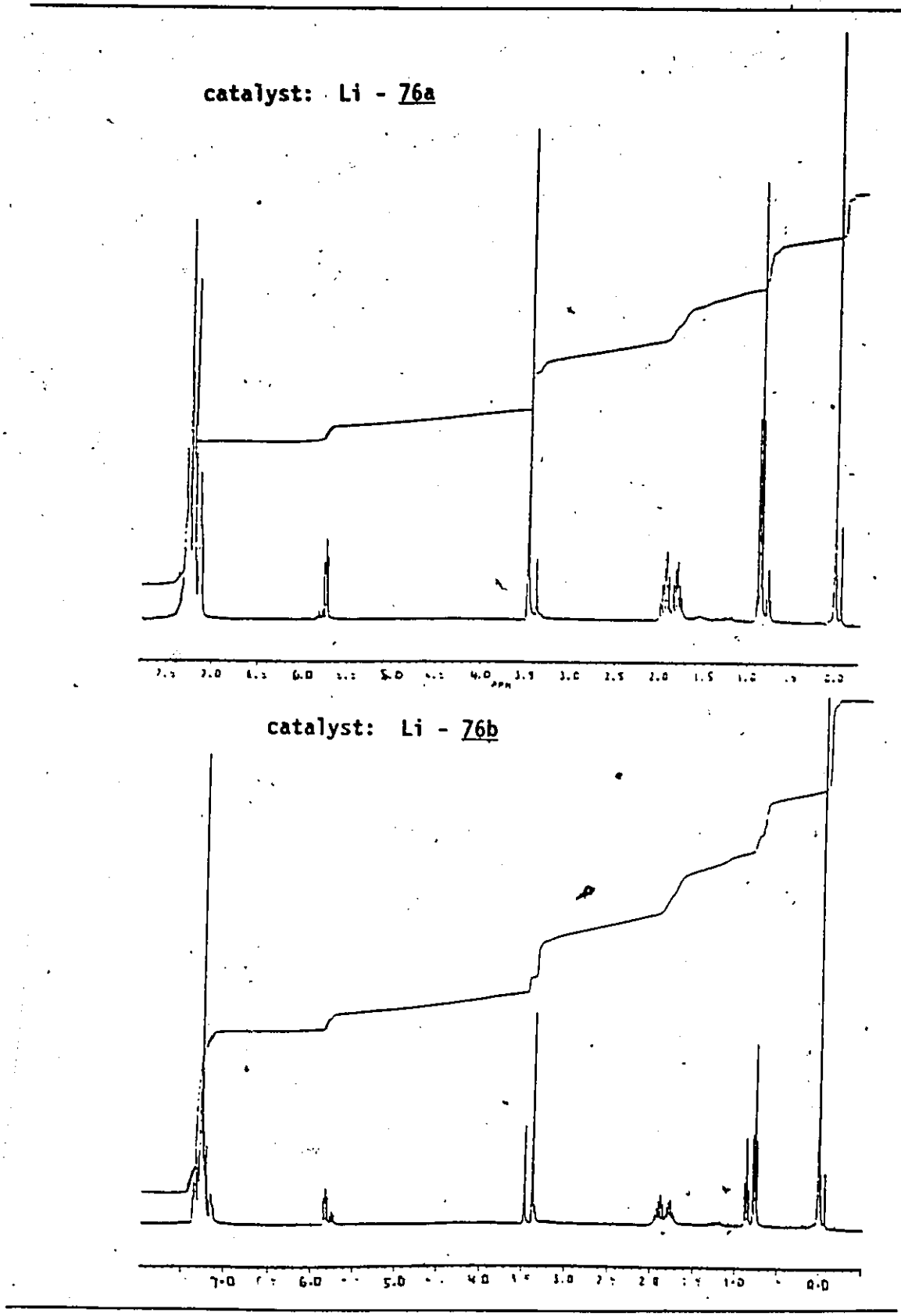


FIGURE 45. ^{1}H NMR spectra of Mosher esters.

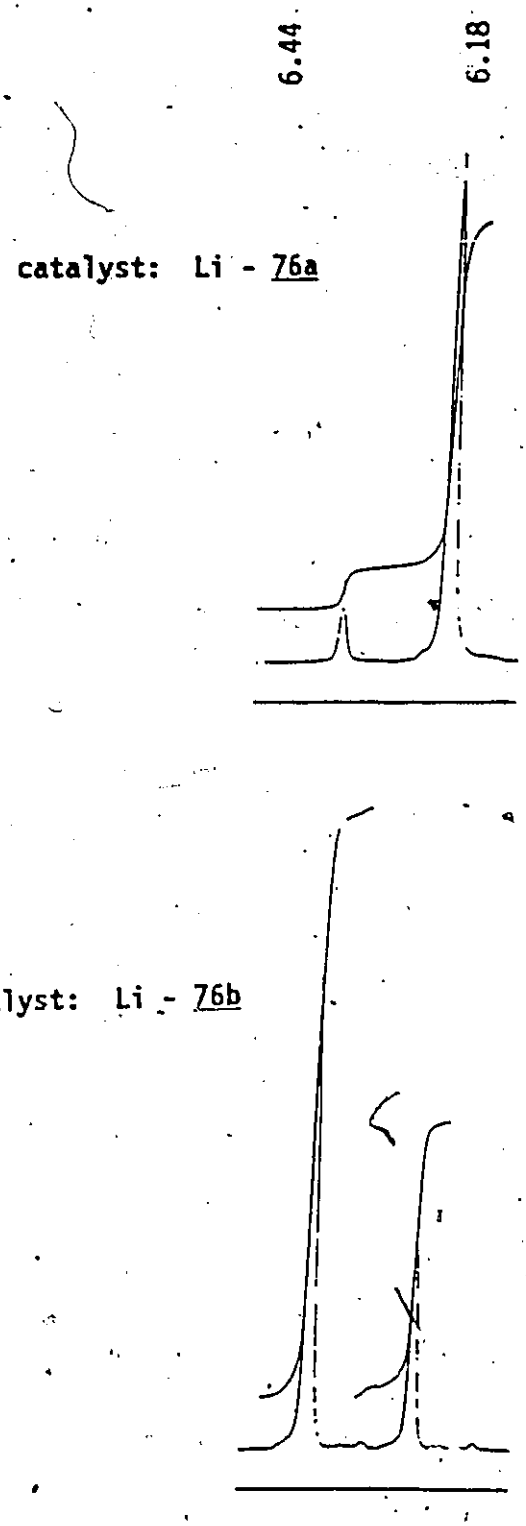


FIGURE 46. ^{19}F NMR spectra of Mosher esters.

76b would be expected to produce the other enantiomer in excess.

The observed differences in the degree of asymmetric induction (84 vs. 38% enantioselectivity for 76a and 76b respectively) can be attributed to the diastereomeric nature of the quinolizidines. This diastereomeric nature expresses itself via important energy differences in the "best fits" of the transition states. As outlined earlier this phenomenon has been observed for the diastereomeric pair of cinchona alkaloid catalysts quinine and quinidine.[3] Noteworthy, in this regard, is the reaction time difference for reaction catalyzed by Li - 76a and Li - 76b *viz.* 23 hours vs. 18 days.

It is important to realize that although the uncatalyzed addition of $Zn(Et)_2$ to benzaldehyde has been reported to be slow (30% complete after 24 hour at room temperature.[19]), it does compete with a slow "catalyzed" reaction. Therefore the 38% enantioselectivity for 76b after 18 days cannot be taken as a true representation of the enantioselectivity of 76b since enantiomeric dilution occurs by the uncatalyzed reaction. We conducted an uncatalyzed "blank" reaction and verified the extent of reaction reported after 24 hours and also found approximately 54% conversion after 18 days. Therefore it is clear that while 76b induces chirality in the reaction it does not accelerate the reaction. In fact the presence of 5 mole percent of quinolizidines 76b, 78a or 78b all markedly *decrease* the reaction rate relative to the blank reaction. Because the product suffers stereochemical dilution due to the uncatalyzed reaction, the actual chirality transfer must be higher than the observed 38%. Thus it may be that a stoichiometric amount of 76b would overcome the apparent low turnover rate and lead to increased enantioselectivity.Such a reaction would require larger quantities of the chiral

amino alcohols 76b or 78a or 78b than were available to us and therefore the reaction was not examined.

Contrary to the previously discussed direct correlation between the configuration at the hydroxy stereocenter of the amino alcohol catalyst and the induced configuration of the predominant enantiomeric product our results indicated a stereochemical cross-over. It can be seen that the R hydroxy isomer (76a) produced the S enantiomer of 1-phenyl-1-propanol in excess while the S hydroxy isomer (76b) produced the R enantiomer of 1-phenyl-1-propanol in excess. At first glance it would appear that either the reaction proceeds via a different mechanism or the original mechanistic concept is incorrect. In fact the answer lies simply in the RS nomenclature used.

Consider the application of the mechanistic concept to 76a and 76b. (Figure 47)

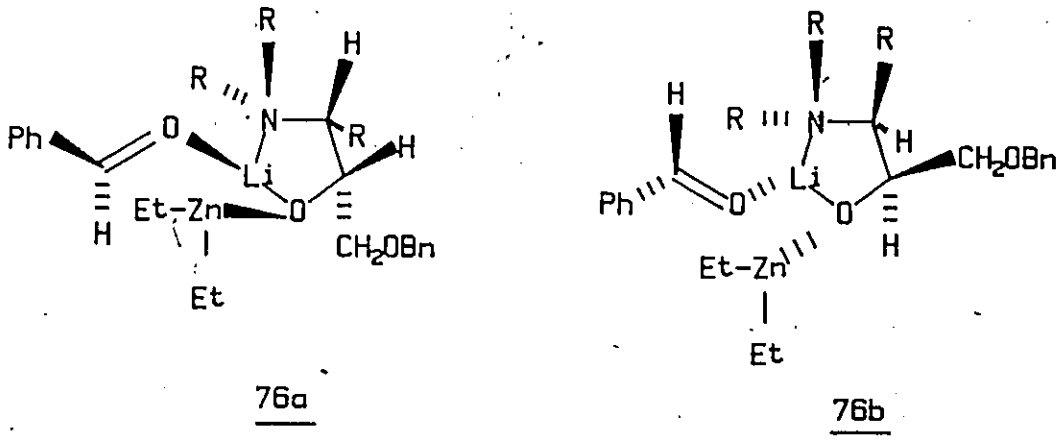


FIGURE 47. Mechanistic concept applied to amino alcohols 76a and 76b.

The benzaldehyde and diethyl zinc are situated anti to the steric bulk at the hydroxy and alpha to nitrogen stereocenters of the catalyst, as in the accepted mechanistic concept. This situation predicts the products observed. But since the stereochemical descriptor of the hydroxy stereocenter changes as a result of the presence of the O-Bn group, an apparent anomaly occurs.

If the O-Bn group is considered as a 3rd chelating position of the amino alcohol there is no change in the configuration of the predicted products. Applying the same mechanistic concept to amino alcohols 78a and 78b also predicts the products observed.

Conclusions

We have prepared two enantiomerically pure diastereomers of each of two substituted quinolizidines (76a, 76b, 78a, and 78b). The solution conformation of these quinolizidines was determined by proton NMR data. Compounds 76a and 78a existed as trans-fused quinolizidines whereas 76b and 78b were present as cis-fused quinolizidines. Given the general utility of various chiral beta-amino alcohols as catalysts in the several previously discussed reactions it seemed worthwhile to test the chiral quinolizidines that we have prepared as catalysts in a selection of these reactions. In this regard, we did attempt to quaternize 76b with benzyl bromide but were unable to isolate any of the quaternary ammonium salt to test as a chiral PTC. Perhaps 76a, 78a, and 78b might provide the desired quaternary ammonium salt under similar circumstances. These would fulfill the requirements for potentially successful PTC's. We did test amino alcohols 76a, 76b, 78a and 78b as catalysts in the diethylzinc addition to benzaldehyde. We determined that these affect the enantioselectivity and the rate of addition of diethyl zinc to benzaldehyde to varying degrees. The best result was obtained with the lithium-salt of 76a which produced the S enantiomer of 1-phenyl-1-propanol in 98% chemical yield in 84% ee. The R enantiomer was obtained in 76% yield and in 58% ee employing 78b as the zinc salt. While these results are encouraging optimization of conditions, such as temperature, solvent studies, or modification of the catalysts, may provide even better results in this addition reaction.

In addition to their potential utility as catalysts the amino diols

78a and 78b may be tested for biological activity since they were found to be water soluble. The biological activity of water soluble amino alcohols is well documented.[62]

CHAPTER II

Alkylation Reactions of Derivatives of the Camphor Imine of t-Butylglycine.

INTRODUCTION

The development and understanding of synthetic methods for asymmetric carbon-carbon bond forming reactions represents an ongoing challenge to the practicing synthetic organic chemist.

Carbon-carbon bond-forming reactions of enolates (e.g. aldol, alkylation) are one important area of asymmetric synthesis. One successful approach to this problem has been the use of chiral molecules known as chiral directing agents. The 3 step sequence involves, as a first step, the preparation and isolation of a chiral intermediate, (imine, hydrazone, etc.) derived from the prochiral substrate. The second step is the reaction (e.g. alkylation) of this chiral intermediate. The presence of the chiral directing agent makes the transition states for alkylation at a prochiral centre diastereomeric and of unequal energy. Therefore asymmetric induction can occur (*cf* Chapter I) and one diastereomer is formed in excess. Removal of the chiral directing agent from the reaction product affords the alkylated substrate in an enantiomerically enriched state. As is the case with a chiral catalyst (Chapter I), the closer and stronger the interaction of the chiral portions of the attached chiral group with the alkylating agent at the transition state, the larger the expected energy gap between the diastereomeric transition states will be and thus the higher the expected stereodifferentiation.

Work on the chiral directing agent approach in asymmetric synthesis began in the late 1960's[67a], but only in the last decade has success (>90% ee) been achieved.[1, 67b] Despite the achievements, some drawbacks are inherent in this approach. The procedure requires three steps and

the use of stoichiometric quantities of chiral auxiliaries which often must be synthesized. However, the use of inexpensive and recyclable chiral adjucts and the wide applicability of this approach make it a reasonable alternative to the catalytic approach. In addition since the products obtained are diastereomers and not enantiomers (as is the case when a chiral catalyst is used) separation and purification is possible and the diastereomeric excess (and thus the enantioselectivity) of the reaction may be determined directly from the reaction products. When enantiomeric products are formed, separations are not possible without the use of chromatography with chiral packings and further reaction forming diastereomers is required in order to ascertain the enantioselectivity of the reaction.

The use of the naturally occurring molecule (+)-camphor (Figure 48) as a chiral directing group for a variety of reactions has proven to be both popular and practical.

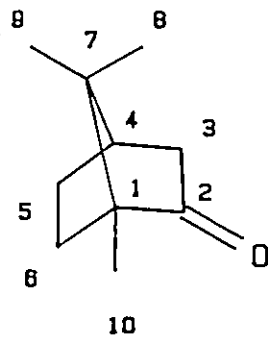


FIGURE 48. R-(+)-camphor

Recent comprehensive reviews[67c] delineating the use of camphor and its derivatives as chiral directing agents in asymmetric synthesis attest to this fact. Two recent Ph. D. dissertations[68, 69] from our

laboratory have centered around the use of camphor as a chiral adjunct for the preparation of chiral amino acids *via* diastereoselective alkylation of the corresponding glycinate imine. Our immediate goal was to elucidate the factors which contribute to the observed diastereofacial selectivity in these reactions.

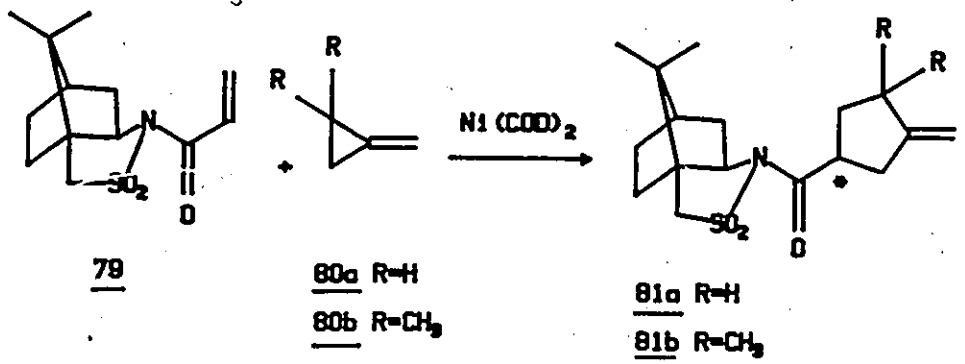
The abundance, crystallinity, rigidity, steric constraints (methyl groups) and possible transformations of (+)-camphor or (-)-camphor are factors which contribute to its popularity and practicality as a chiral directing agent. In addition the products derived employing camphor are frequently crystalline and can often be obtained diastereomerically pure by recrystallization.

Oppolzer's reviews[67c] thoroughly summarize the literature concerning the use of camphor as a chiral directing group up to the middle of 1986. Papers featuring camphor in this role have continued to appear in the literature since that time and those papers will be the focus of this review.

Binger has utilized Ni(0)-catalyzed [3 + 2] cycloaddition of (-)-camphorsultam-acrylate (79) with methylene cyclopropane (80a), 2, 2-dimethyl methylene cyclopropane (80b) to obtain 3-methylene cyclopentane carboxylic amides (81a) 81b).[70] (Figure 49)

Under optimum conditions (-20° C, 16 hours, toluene) 81a is obtained in 65% yield and 91% de from 80a and 79. The dimethyl analogue 81b was obtained in 85% chemical yield and 98% de (0° C, 20 hours). On the basis of Oppolzer's results, the authors assigned the new stereocenter formed as the S configuration.

Taber, *et al.* have described the use of the camphor derived alcohol, 82 (Figure 50) as a chiral agent in several reactions.[71-73]



79

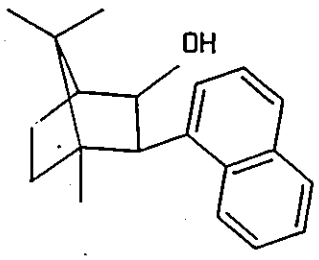
80a R=H

80b R=CH3

81a R=H

81b R=CH3

FIGURE 49. Cycloaddition reaction.[70]



82 = R*O-H

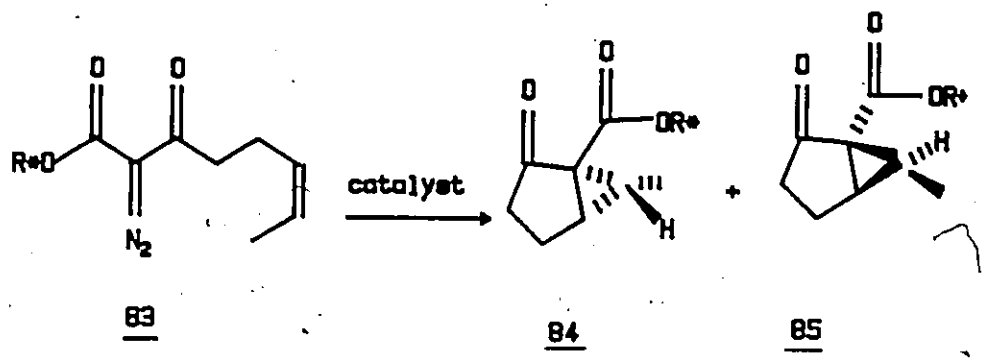
FIGURE 50. Camphor-derived chiral directing alcohol.[71]

Taber[71] has reported an intramolecular cyclopropanation reaction of 83 directed by 82 and catalyzed by (dppp) $PdCl_2$ proceeded with diastereofacial selectivity (de = 60%) giving 84 as the major product in 64% yield. (Figure 51)

The stereochemical course of the reaction was rationalized as proceeding through the intermediate shown in Figure 52.

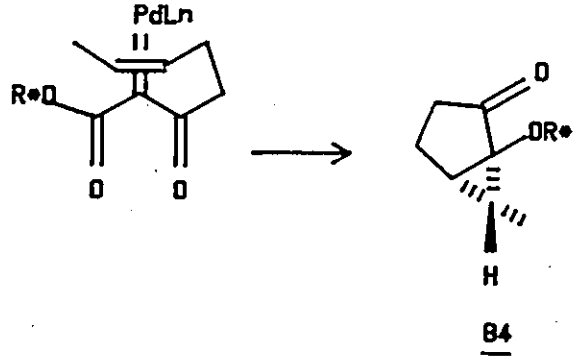
As the olefin approaches one face of the metallocarbene to form an intermediate metallocyclobutane, the transition metal, with its ligands

will be pushed out from the opposite face. Thus, the olefin preferentially approaches the more hindered face of the metallocarbene, between the aromatic ring and the beta-keto ester.



83 84 85

FIGURE 51. Intramolecular cyclopropanation.[71]

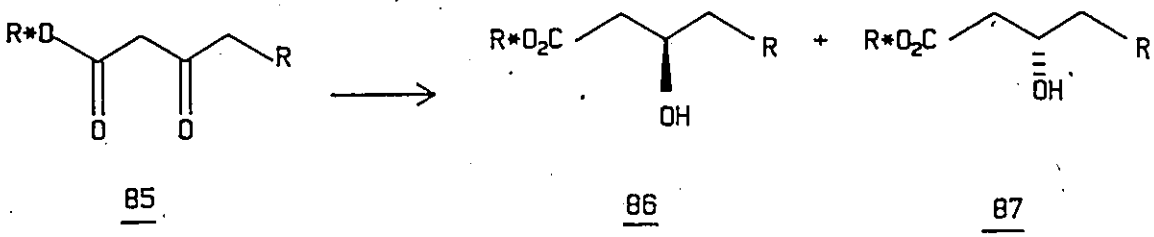


84

FIGURE 52. Stereochemical rationale of cyclopropanation.[71]

To confirm the relative and absolute stereochemistry of the cyclopropanation 84 was converted to enantiomerically pure (+)-isoneonepetalactone.[71]

Taber took advantage of the structural features of alcohol 82 to obtain highly stereoselective hydride reductions of beta-keto esters.[72] The alcohol 82 is designed to block one face of the carbonyl of the corresponding beta-keto ester 85. Depending on the conditions employed for the reduction, either diastereomer (86 or 87) can be obtained in excess. (Figure 53)



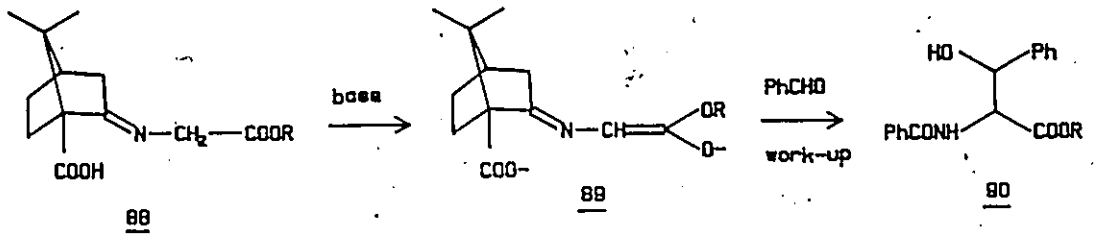
85 86 87

FIGURE 53. Reduction of beta ketoester.[72]

When hydride reduction proceeds *via* the transition state in which the carbonyls are *syn* ($ZnCl_2/Zn(BH_4)_2$), diastereomer 86 is obtained in 84% de. In contrast an *anti* orientation of the carbonyls (Dibal BHT) produces diastereomer 87 in 92% de. Reduction (LAH) of the ester moiety produces a chiral 1,3-diol suitable for use in asymmetric synthesis and regenerates the chiral agent. Taber has applied this methodology to the stereoselective preparation of a wasp pheromone[72] and a biologically active piperidine alkaloid.[73]

Asymmetric preparation of beta-hydroxy, alpha-amino acids (90) (threo and erythro beta-phenyl serines) using (+)-ketopinic acid as the chiral auxilliary has been reported.[74] (Figure 54) Benzaldehyde was condensed with the metal (Li^+, K^+, Zn^{2+}) dianion enolate, 89, of the

chiral imine 88 to give, after hydrolysis and derivatization, beta-phenylserine in chemical and optical yield which depended the ester group (R = CH_3, Et, t-butyl) and the metal used.



88 89 90

FIGURE 54. Preparation of beta-hydroxy, alpha-aminoacids.[74]

It was found that a small cation (Li^+, K^+) and large ester group favour the enantiomeric enrichment and chemical yield of the threo isomer (best case example R = CH_3, K^+, ee = 60%). In contrast the zinc cation provides similar chemical yield of the erythro and threo isomers but gives enantiomerically enriched erythro forms (ee = 50% ex. R = C_2H_5, Zn^{2+}). The structure of the bimetallic (Li^+, K^+) or mono metallic (Zn^{2+}) intermediate enolate determines the steric course of the reaction and thus the stereoselectivity.

In our laboratory camphor has proven to be a valuable chiral agent in the alkylation of lithiated t-butyl glycinate imine by various alkylating agents. The reaction provides alpha-amino acids of known configuration and predictable optical purity.[68, 69, 75] (Figure 55) Alpha amino acids[76] are both biologically active compounds and important members of the chiral pool[77] thus many strategies have been devised for their synthesis.[68, 69]

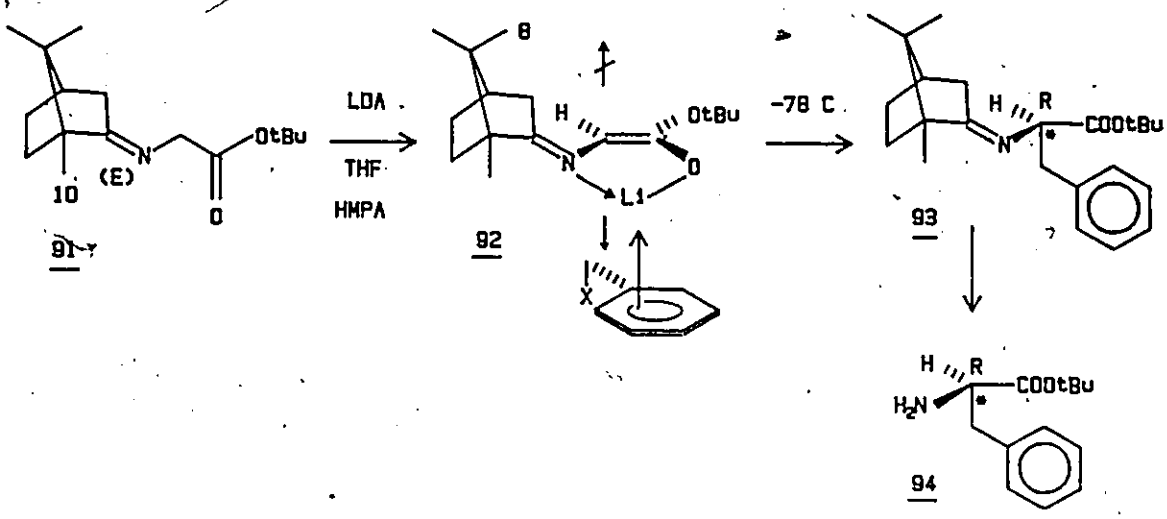


FIGURE 55. Alkylation of camphor imine.

Condensation of t-butylglycine and camphor thione produced the (E)-imine (91) selectively owing to the steric influence of the C(10) methyl group. The conformation of the enolate formed from the imine and lithium diisopropyl amide (LDA) is assigned the chelated structure 92. The diastereofacial selectivity in the alkylation of this enolate is dependent on the structure and electronic nature of the electrophile. Attack of an allylic or benzylic halide from the less sterically hindered *re* (bottom face opposite the C (8)-methyl) of the enolate generates the (2R)-imines (for example 93) in 69 to greater than 98% de. Transamination of the benzylated imine produced the R-phenylglycinate (94). However, aliphatic electrophiles reacted with the enolate more slowly than did the allylic (or benzylic) electrophiles and with only 0-60% stereofacial differentiation.

Two facts confirm that these alkylation reactions produced only

kinetic products. No dialkylated reaction products were detected in the reaction regardless of the electrophile or the number of equivalents of base employed. Second, attempted deprotonation of the monobenzylated material followed by D_2O quench led to no deuterium incorporation in the product indicating that a second deprotonation is not possible. Seebach's observations[77b] on the lack of deuterium incorporation when lithium-enolates are quenched with D_2O may bear on the interpretation of this observation. However, the complete lack of deuteration (as determined by mass spectrometry) makes it most unlikely that a second deprotonation can occur.

In general the reactions are conducted at low temperature (-78° to -20°C) in THF solvent in the presence of the additive hexamethylphosphoramide (HMPA). The presence of HMPA was found to facilitate the alkylation process. The exact origin of this facilitation remains unclear. Experimentally the highest chemical and optical yields using the methyl glycinate ester were obtained when one equivalent of HMPA is added to the reaction. (Table 5) This may be due to deaggregation of the lithium enolate.

TABLE 5

The Influence of HMPA on Chemical and Optical Yields[68]

Equiv HMPA	Yield(%)	Diastereomer ratio
0	40	1:3
1	73	1:3
2	70	1:2

Stereoelectronic interactions between the allylic (benzylic) system of the electrophile and the enolate system have been invoked to rationalize the enhanced diastereofacial selectivity observed with these electrophiles relative to the saturated ones (Figure 55). The diastereofacial selectivity observed when saturated electrophiles are employed is attributed solely to the steric interactions between the electrophile and the C(8)-methylgroup of the camphor moiety. The preference for the *re* face alkylation therefore arises strictly as a result of the increased steric interaction at the *si* face. However, if the R group of the electrophile is forced to reside over the lithium-enolate system (eclipsed form) and therefore closer to the camphor moiety, the steric interactions on the *si* face are increased much more than those on the *re* face. (Figure 55) It has been postulated that either an attractive pi-pi interaction or pi-metal interaction enforces the eclipsed form and leads to the observed diastereoselection (*re* face attack) and diastereoselectivity (69-98%). Support for this postulate was obtained when the enolate was alkylated with 2 mole equivalents of racemic 1-phenylethyl bromide or 3-bromocyclohexene and found to give clean kinetic resolution of the halide to form (2R)-esters containing a second, diastereomerically pure center at C(3).

Previous attempts to perform aldol reactions on the camphor imine lithium enolate have been unsuccessful. Mishra[68] attributed the lack of reactivity of benzaldehyde and the enolate 92 to the "softness" of the enolate. This concept, first enunciated by Pearson[78], states that soft bases react with soft acids and hard bases with hard acids. Since the camphor imine enolate is a soft base and the carbonyl carbon of an aldehyde is a hard acid no reaction is expected. Stork[79] applied this

principle to account for the experimentally observed preference for 1, 4-addition over 1, 2-addition of imine enolates to conjugated ketones and to explain the lack of aldol reaction between aldehydes and the enolate of ethyl N-benzylidine glycinate. Leavitt[69] invoked a similar rationale to explain the lack of reaction between the camphor imine enolate and styrene oxide.

On the other hand, a successful aldol type reaction has been reported[74] employing imine of type 88. The presence of an oxygen anion in the CDA seems to facilitate the aldol reaction relative to monoanion systems.

The present investigation was aimed at answering two questions. The first question concerns the importance of the methyl groups on the camphor moiety in obtaining high diastereofacial selectivity with unsaturated electrophiles. Can the electronic interaction alone account for the high diasterofacial selectivity in the alkylation of the camphor imine of t-butylglycine with benzyl bromide? Or, are both the electronic interaction and steric effects (from the methyl groups) required for the enhanced diastereofacial selectivity?

The second question concerned the effect of a dianion in the camphor moiety on alkylation reactions of the corresponding t-butylglycine imine. Specifically would alkylation of such a dianion enolate with benzyl bromide still provide essentially 100% de. Further, would the presence of the dianion on camphor facilitate an aldol reaction with benzaldehyde?

RESULTS AND DISCUSSION

Preparation and alkylations of the norcamphor imine of t-butylglycine

Our first goal was to determine the importance of the methyl groups on the camphor moiety of the corresponding t-butylglycine imine in obtaining high diastereofacial selectivity in the alkylation reaction with unsaturated electrophiles. To this end we prepared the norcamphor imine of t-butylglycine (97). (Figure 56) The absence of any methyl

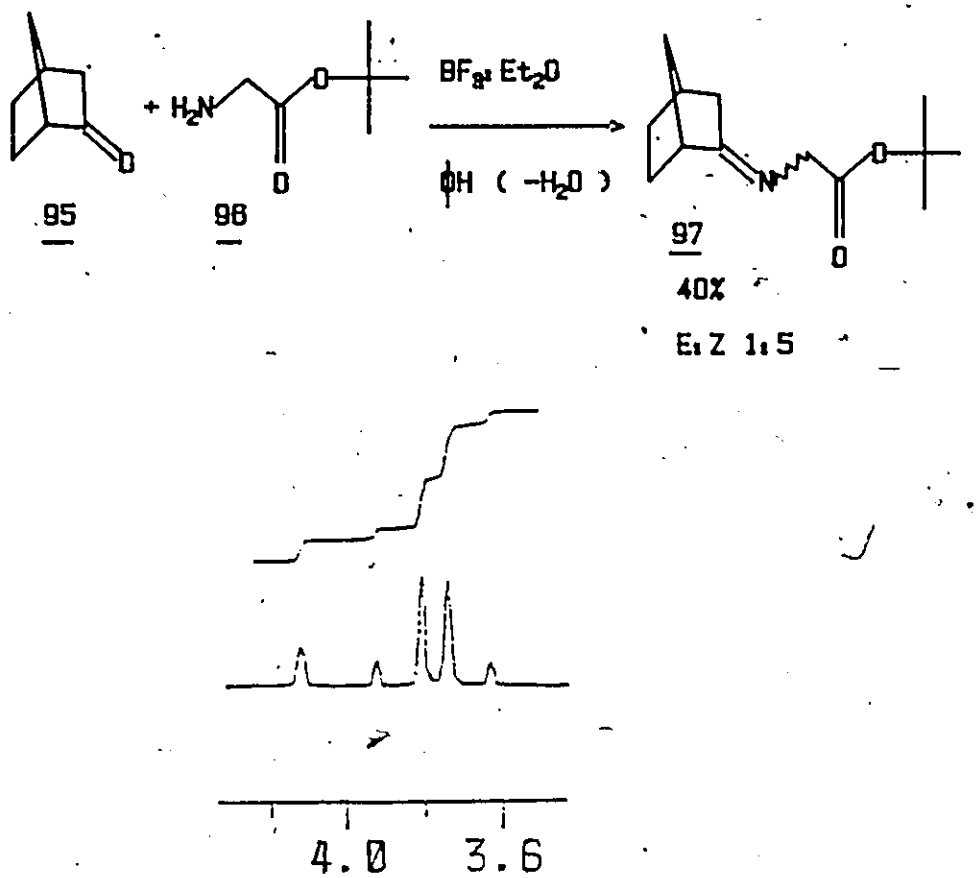


FIGURE 56. ^1H NMR of C-2 protons of norcamphor imine.

groups at C(7), C(8), C(10) of norcamphor make this the ideal imine to study in order to ascertain the stereochemical role of the methyl groups of the corresponding camphor imine. Reaction of racemic norcamphor (95) with t-butylglycine (96) in benzene containing a catalytic amount of $BF_3:Et_2O$ with removal of water produced the requisite imine 97. The imine was obtained in 40% yield after purification by distillation. The proton NMR spectrum of the methylene imine protons of the glycine moiety (δ=3.89, 4.08) indicated a 5:1 ratio of geometric isomers (E, Z) at the imine double bond. (Figure 56) Examination of molecular models suggests that the Z stereoisomer should be expected to be the predominant form which is opposite to the case of camphor. The difference is due to the lack of a C-10 methyl group in the norcamphor case. All attempts to separate these stereoisomers by chromatographic means resulted in the hydrolysis of the imine double bond. Therefore we were unable to separate the diastereomers. However alkylation of this mixture can still provide diastereomerically enriched product if the reaction is facially selective, as in the case of the camphor imine.

The alkylation reactions of the enolate of norcamphor imine 97 were conducted in THF at -78° C in the presence of one equivalent of hexamethylphosphoramide and employing benzyl bromide as the alkylating agent.

As indicated in Table 6, we determined that one equivalent of HMPA was required to give the maximum chemical yield of phenylalanine t-butylester (85%). (Figure 57)

This result is analogous to the previously reported[68, 69] trend. After chromatography on silica gel, only the hydrolyzed alkylated product phenylalanine t-butylester (98) was isolated and the ^1H NMR of

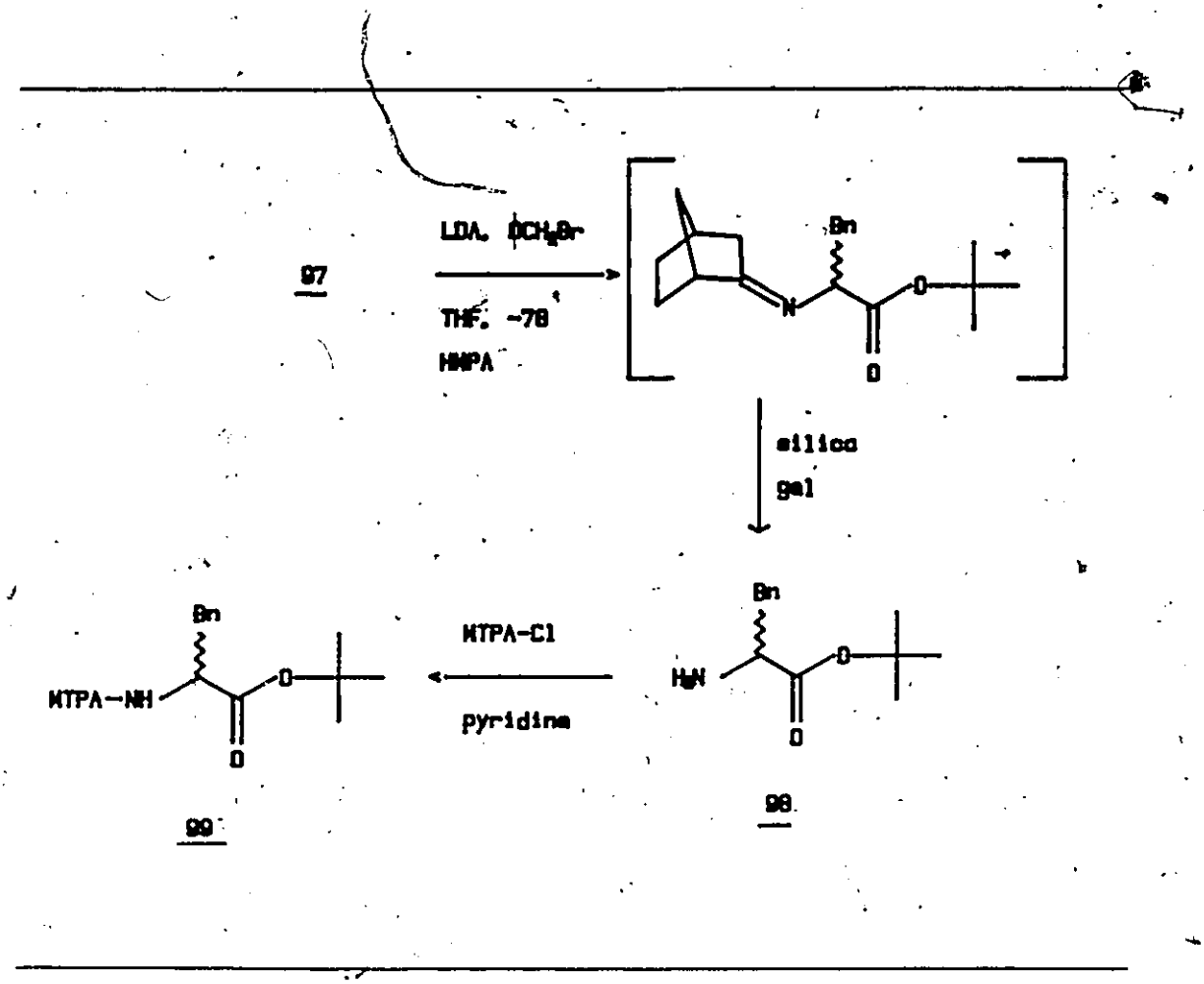


FIGURE 57. Alkylation of norcamphor imine.

the derived Mosher esters showed this to be racemic as expected. Since racemic norcamphor had been employed to prepare the imine, diastereofacial selectivity in the alkylation provides four possible stereoisomers related as two diastereomeric pairs of enantiomers (RS,SS,SR and RR). Each pair of enantiomers is obtained by attack from the same face of either enantiomer of the norcamphor imine. In theory the two racemic diastereomers which are generated by top face or bottom face attack should exhibit different NMR spectra and thus allow calculation of the diastereomeric excess by integration of the methine proton. However, hydrolysis of the alkylated product during chromatography resulted in the loss of distinction between the two diastereomers and a racemic

mixture of enantiomerically related alkylation products was obtained and no information on the stereochemistry of alkylation could be obtained. Therefore we were forced to examine the proton NMR of the crude reaction mixture in order to determine if any asymmetric induction occurred. The ^1H NMR showed 8 overlapping peaks for the imine methine proton indicating that both diastereomers were present. Unfortunately none of the eight peaks was of significantly greater intensity than the others and the overlapping nature of the peaks made the accurate determination of diastereoselectivity impossible. However, in the best scenario, little stereoselectivity is evident.

TABLE 6. Influence of HMPA on chemical yield.

Eq HMPA	Chemical Yield	Optical Yield (Mosher Amide)
0	75	0%
1	85	0%
2	61	0%

Thus it appears that in addition to the proposed electronic effect the methyl groups are important in obtaining high diastereofacial selectivity in the alkylation reaction of the camphor imine of t-butylglycine by benzylic electrophiles. This may be attributed to the greater steric constraints imposed by the methyl groups on both the imine stereochemistry and the direction of electrophilic attack coupled with the pi-Li electronic effect present when benzylic halides are employed as alkylating agents. Future work should include employing carbon skeletons with

intermediate numbers of methyl groups to determine which methyl groups are important in the alkylation of their respective imines with ^{t}butyl glycinate.

Preparation and Alkylation of the Imine of Alcohol 100

We prepared imino alcohol 101 (Figure 58) in order to study the effect of a dianion on the diastereofacial selectivity of alkylation reactions employing benzyl bromide as the alkylating agent. The imine 101 was prepared in 65% yield via the Lewis acid catalyzed condensation of 11-hydroxymethylcamphor (100) and t-butyl glycinate (96) in benzene with removal of water. Interestingly, direct formation of the hydroxy camphor imine was possible by this method. Previously the camphor imine had been prepared via the camphor thione because very little product was formed under similar Lewis acid conditions.[68] However, more recently we and others[80] have been able to use the conditions for the formation of 91, thus avoiding the requirement for preparing the thione.

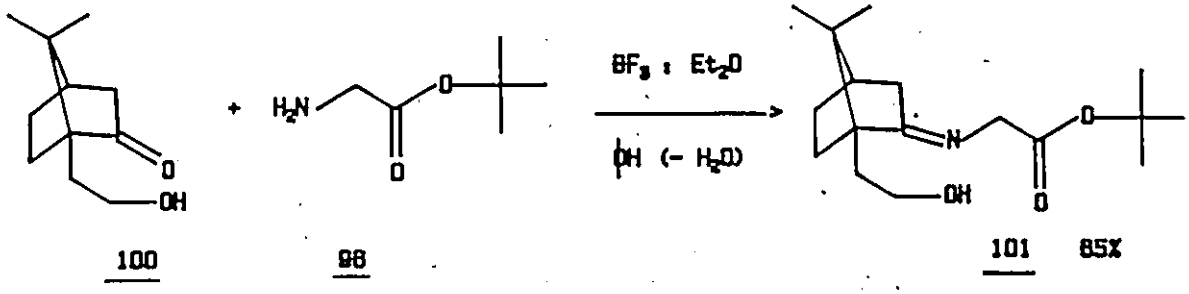


FIGURE 58. Preparation of 10-hydroxymethylcamphor imine.

The absence of extra peaks in the ^{13}C or ^{1}H NMR indicated that only one diastereomer had been obtained. This was assigned the E con-

figuration at the imine double bond owing to the steric influence at C-10 in analogy with the camphor imine. 11-Hydroxymethylcamphor (100) was prepared as outlined in Figure 59.

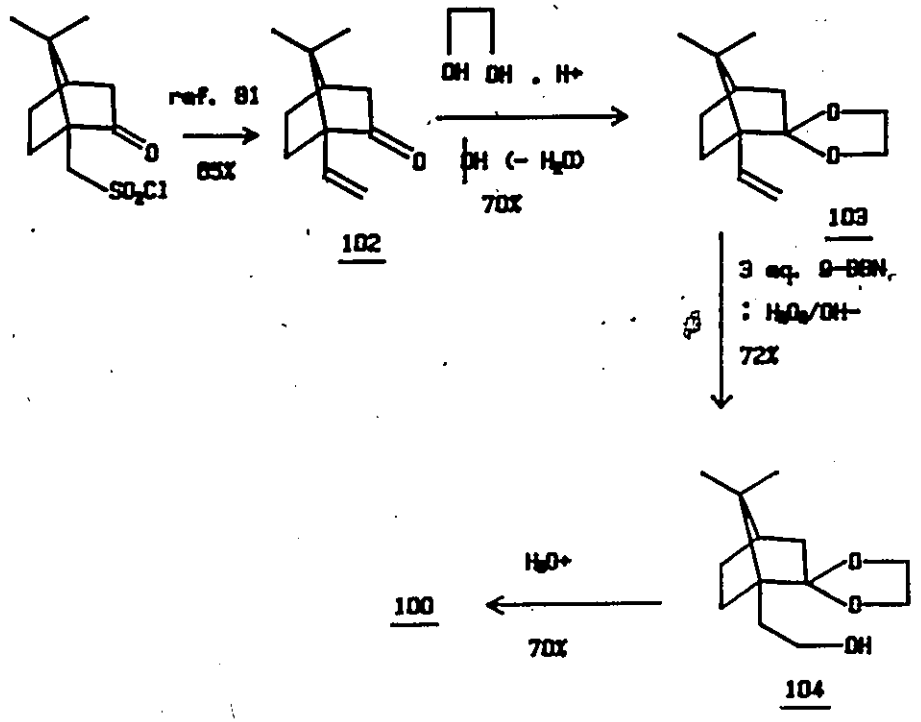
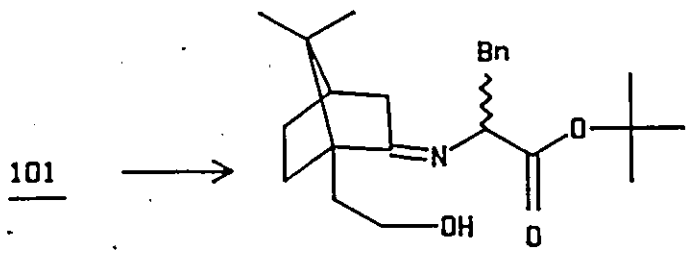


FIGURE 59. Preparation of 10-hydroxymethylcamphor.

Vinyl Camphor (102) was obtained in 65% yield from (+)-10-camphorsulfonyl chloride and diazomethane via pyrolsis of the corresponding episulfone.[81] Protection of 102 as its ethylene ketal gave a 70% yield of 103. Hydroboration of 103 with 9-BBN[82] followed by a basic peroxide work-up gave the protected alcohol 104 in 73% yield. Three equivalents of 9-BBN were required for complete conversion of 103 to 104. Finally hydrolysis of 104 gave a 70% yield of 11-hydroxymethylcamphor 100.

Attempts to prepare 100 from 102 directly, without going through the protection-deprotection reactions resulted in low yields of 100 accompanied by an inseparable impurity.

The benzyl bromide alkylation reactions of the hydroxy imine 101 were conducted in THF at -78° C employing 2.1 equivalents of LDA. (Figure 60) The results obtained were similar to those outlined in Table 6. Addition of 1 equivalent of HMPA provided the maximum chemical yield of alkylated product 105 (83%) (Table 6).



105

FIGURE 60. Alkylation of 10-hydroxymethylcamphor imine.

TABLE 7. Results of Alkylation of 10-hydroxymethyl camphor imine with Benzyl Bromide

	Yield		Time
Eq. HMPA	Chemical[a]	DE%	(h)
0	37 (64)	78	2.5
1	58 (83)	80	1.5
2	54 (77)	80	1.5

(a) the yield based on unrecovered imine is in brackets.

However, in each case, the diastereomeric excess of 105 obtained was relatively constant (*ca* 80%) which is a lower value than that obtained employing the camphor imine (98%). Therefore, the presence of the dianion at this specific position of the camphor decreases the diastereofacial selectivity of benzyl bromide alkylations. While the exact reason for the reduction in diastereomeric excess in the dianion system relative to the monoanion is unknown, it is possible that the planar 5-membered N-Li-enolate chelate is disrupted by the presence of the O-Li thus allowing a freer rotation of the enolate. (Figure 60a, A) Alternatively it may be that the C-10 side chain hinders attack at the *re* face of the enolate thus making *si* face attack more competitive. (Figure 60a, B) Interestingly, recrystallization of the reaction product did not alter the diastereomeric excess appreciably.

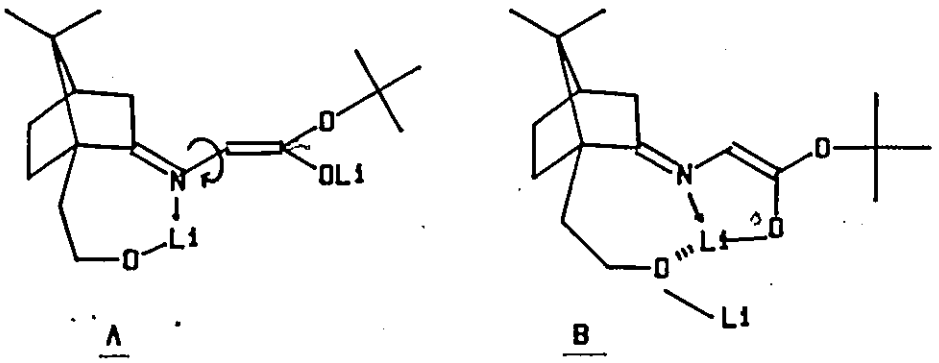


FIGURE 60a. Possible structures for the dianion of 101.

The integration and chemical shift of the ^1H NMR of the product methine proton indicate: 1) the de of the reaction and 2) the reaction proceeds in a stereochemical manner analogous to the camphor imine.

(Figure 61) The methine proton appears as a doublet of doublets (= 3.99 ppm) with the minor diastereomer appearing at lower field as is the case of the camphor imine alkylations. Integration of the partially overlapping peaks allows a calculation of the diastereomeric excess. On the basis of our previous work[75] which showed that the product of *si* face attack on the camphor imine showed its methine proton absorption at lower field that the product of *re* face attack, the major isomer obtained in this study can also be assigned as the product of *re* face attack. This could be confirmed by transamination of the imine and comparison of the sign of the optical rotation of the phenylalanine t-butylester with a sample of known absolute configuration.[68]

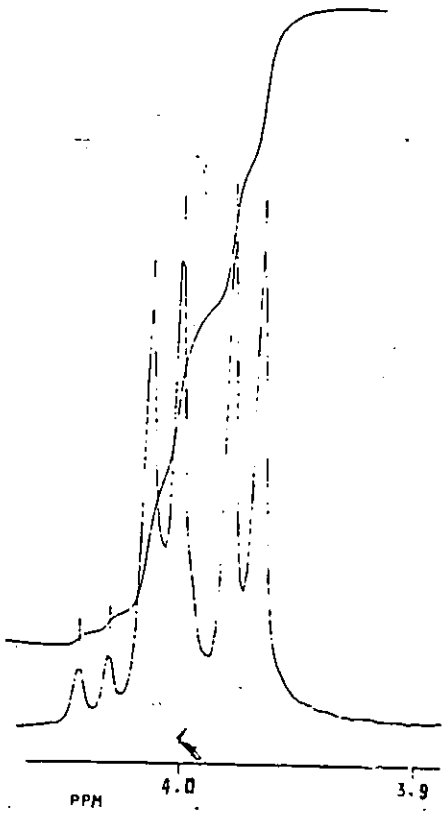


FIGURE 61. ^{1}H NMR of C-2 protons of benzylated hydroxymethylcamphor imine

As our final reaction of the dianion of glycinate 101 we decided to explore an aldol reaction with benzaldehyde. Previous attempts by Mishra and McIntosh[68] yielded no aldol products when the camphor imine was employed. This fact was attributed to the "softness" of the enolate system. Recently aldol reactions to 91 have been reported to proceed under PTC conditions with an electron withdrawing group (e.g. p-NO_2) on the the aryl portion of benzaldehyde.[80] However, we isolated a 71% yield of of the aldol product 106 (Figure 62) from benzaldehyde and when the dianion of imine 102 was employed.

The aldol reaction creates two new chiral centers and therefore four diastereomerically-related products are possible. These are the *erythro* and *threo* forms arising for each of *re* and *si* face attack on the enolate. In the examination of the product mixture obtained, it was found that the stereoisomers could be separated into pairs. Whether these are the *erythro/threo* pair resulting from *re*-face or *si*-face attack, or whether they are the *re/si* pair both having the *erythro* or *threo* configuration has not been determined.

The ^1H NMR spectrum of the crude aldol reaction product indicated a 7:1 ratio of pairs of diastereomers as indicated by integration of the hydroxy methine proton. We successfully separated the pairs of diastereomers employing silica gel chromatography as indicated by the proton NMR spectra of the major (56% yield) and minor (15% yield) pair. However, we can make no assignment as to the stereochemistry of these products at this time. Such investigation will be the subject of future work. Interestingly, the minor pair of diastereomers appear to be present in approximately equal amounts according to the ^1H NMR. However, the major pair seem to be present as at least a 2:1 mixture of

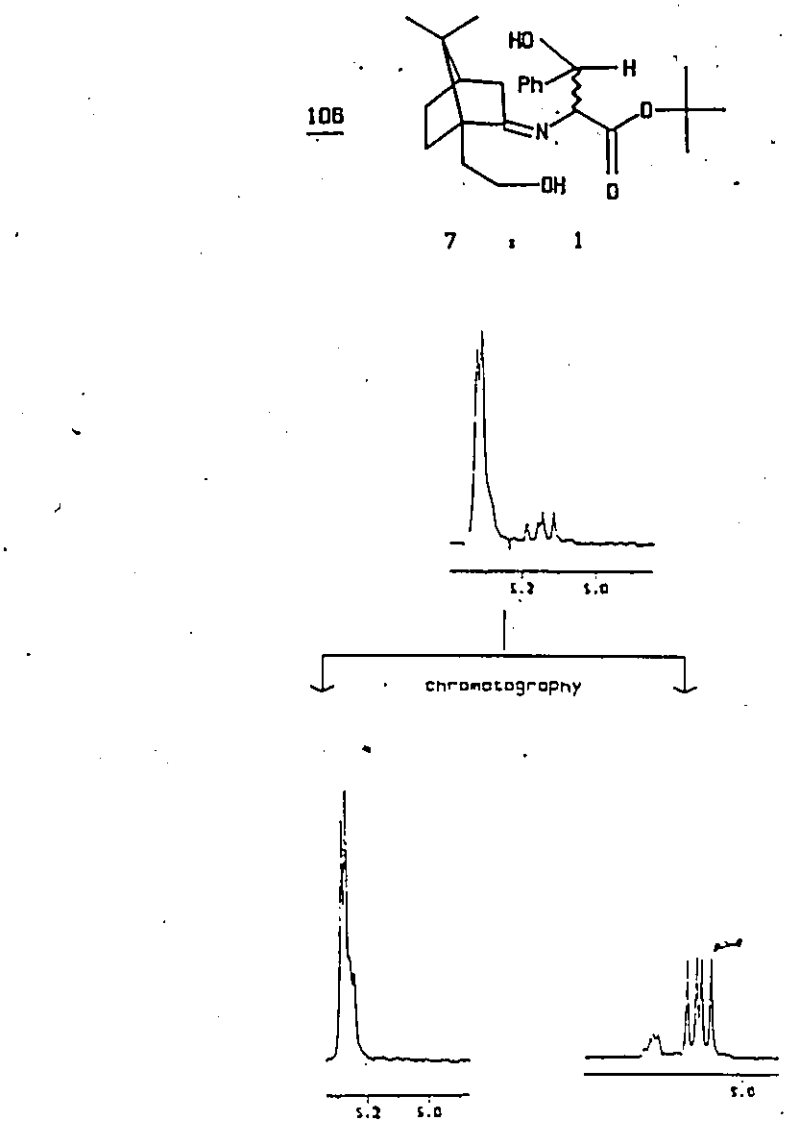


FIGURE 62. ^{1}H NMR of aldol product from hydroxymethylcamphor imine.

diastereomers. It seems that the presence of a dianion in the enolate system facilitates the aldol reaction of these imine systems with benzaldehyde. In contrast the mono anion (camphor imine) does not undergo an aldol reaction with benzaldehyde. The exact nature of the

facilitation is unclear at this time. However, it is possible that a lithium atom of the dianion system can coordinate to the aldehydic oxygen thus activating the carbonyl and making it more reactive with the imine.

Future work in this area could include employing different metal salts and different ester groups. Stereoselectivity in reactions with other dianion systems have been found to be dependent on these two parameters.[74]

Conclusion

We have prepared the norcamphor imine of t-butyl glycinate and found that the alkylation reaction of the corresponding lithium enolate with benzyl bromide proceeded with no diastereofacial selectivity. This indicates that the results previously obtained with camphor as the CDA depend critically on the presence of the three methyl groups.

The t-butyl glycinate imine of 11-hydroxymethylcamphor was prepared and found to exist as the E geometric isomer. Alkylation of the corresponding dilithium enolate with benzyl bromide proceeded with 80% diastereoselectivity regardless of the quantity of HMPA employed.

The dilithium enolate of the imine of 11-hydroxymethylcamphor was found to undergo an aldol reaction with benzaldehyde to give a mixture of stereoisomers.

Future work might include determining the scope and limitations of the aldol reaction of the hydroxylated imine 101, extension of the investigation to other hydroxylated imines, and determining the effect of changing the metal.

CHAPTER III

Experimental and References

EXPERIMENTAL

Synthesis of 4-substituted quinolizidines

General

Unless otherwise noted, infrared spectra were run as neat liquids on a Nicolet 5DX spectrometer and only the four most intense peaks are reported. The NMR spectra were run on a Bruker AC 300 Spectrometer at 300 MHz for ^{1}H, 75 MHz for ^{13}C and 188 MHz for ^{19}F in $CDCl_3$ solution. Values in brackets ([]) are for the minor diastereomer. Where DEPT editing of the carbon spectra was done, the multiplicities that would have been seen in the off-resonance spectra are indicated. The ^{19}F NMR shifts were measured relative to internal trifluoroacetic acid. Dr. C. Rogers (Bruker Spectrospin) performed the C-H correlated 2-D spectra. Optical rotations were measured at 24° C in $CHCl_3$ solution with c=1.0 unless otherwise noted. Optical rotations were performed on a Nicolet polarimeter at Wayne State University, Detroit, Michigan Gas chromatographic analyses were performed using a 1.5 ft x 1/8 in column packed with 5% OV-101 on Chromosorb W or a 8 ft x 1/4 in packed with 20% SE-30 on Chromosorb W. Column chromatography utiliized silica gel 60. Mass spectra were run in the electron impact (EI), field ionization (FI) and fast atom bombardment (FAB) modes. Solvents were removed under reduced pressure and the drying agent used was anhydrous magnesium sulfate. THF and dimethoxyethane (DME) were dried over potassium and benzophenone, ethanol was distilled from magnesium ethoxide, methylene chloride and carbon tetrachloride were distilled from P_4O_{10} and stored over activated molecular sieves. Benzene was dried over sodium metal. *tertiary*-Butyl hydroperoxide in toluene was prepared as described [48c], titanium isopropoxide was distilled and stored under nitrogen. Pyridine was dried by

storage over KOH and distillation under nitrogen. The t-butylester of glycine was prepared as previously outlined.[75] (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid, 2-picoline 4-chlorobutyryl chloride, Norcamphor, BF_3:Et_2O, (+)-10-camphor sulfonyl chloride and 9-BBN were used as received from the Aldrich Chemical Co. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of Mosher Amides and Esters

In general these reactions were run[57] by adding 20 mg of the alcohol or amine to a flame dried vial containing 500 ul of pyridine, 500 ul of CCl_4 and 1.3 mol equivalents of (+)-MTPA-Cl[48b] and stirring 24 hours at room temperature. Work-up involved addition of 5 ML H_2O followed by 20 mL diethyl ether. Separation of the organic layer and washing successively with dilute HCl, dilute $NaHCO_3$, water and brine gave after drying and concentration, a quantitative yield of the Mosher derivative.

1-(α-pyridyl)-3-propanol (61)

This compound was prepared according to the Organic Synthesis[52] procedure in 35% yield from 2-picoline; b.p. 133-140° C (10-11 mm) (lit.[52] 116-118/4mm); ^1H NMR: 8.4 (1H, d(b)), 6.9-7.7 (3H, m), 5.5 (1H, s(b)), 3.6 (2H, t, J = 7 Hz), 2.9 (2H, t, J = 7 Hz), 2.0 (2H, quin., J = 7 Hz).

2-(3-propanol)-piperidine (62)

This compound was prepared in 76% yield by hydrogenation of 61 at high pressure[63] (1300 psi) and temperature (135° C) employing 10% Pd/C as a catalyst and H_2O as the solvent. After saturation of the Celite-filtered solution with K_2CO_3, the oil 62 was recovered by phase

separation and distillation; bp 95-99° C (.85 mm) (lit.[63] 93-94° C 0.6 mm.) ^{1}H NMR: 3.9 (2H s(b)), 3.6 (2H, t, J = 7 Hz), 3.3-2.3 (3H, m), 1.5 (10H m(b)).

Preparation of ester 63

A solution of 3.1g (.031 mol) of 62 in 9.56g (.067 mol) of acetic anhydride was refluxed for 4 hours. After removal of acetic acid and excess acetic anhydride *in vacuo*, distillation gave 4.67g (95%) yield of 63 as a pale yellow oil. b.p. 139-145° C (0.35 mm); IR 2960, 1750, 1640, 1040cm^{-1}, ^{1}H NMR: 4.0 (2H, t(b)) 3.5-2.5 (3H, m), 2.1 (3H, s), 2.05 (3H, s), 1.9-1.3 (10H m(b)). MS(FI): m/z = 227; Anal. Calcd. for $C_{12}H_{21}NO_3$ C, 63.41; H, 9.31. Found: C, 63.11; H, 9.50.

Preparation of alcohol 64

To a solution of 0.524g (.013 mol) NaOH in 15 mL of methanol was added 2.29g (.010 mol) of 63 and the solution was stirred at ambient temperature for 24 hours. Solvent removal *in vacuo* left an oily solid which was extracted with methylene chloride (6 x 10 mL). Chromatographic purification (9:1 acetone:petroleum ether) of the crude oil obtained after drying and removal of the solvent, gave 64 as a colorless oil; 1.87g (65%). IR: 3399, 2935, 1618, 1435, 1065cm^{-1}; ^{1}H NMR:3.6 (2H, t, J = 6 Hz), 3.0-2.5 (3H, m), 2.05 (3H, s), 1.55 (10H, s(b)). MS(FI): m/z = 185. Anal Calcd. for $C_{10}H_{19}NO_2$:C, 64.83; H, 10.34. Found: C, 63.54; H, 10.65.

Preparation of tosylate (65).

To a pyridine (5mL) solution of 0.47g (2.43 mmol) of toluene sulfonyl chloride at 0° C was added 0.45g (2.43 mmol) of 64. After stirring 5 hours at 0° C 20 mL of methylene chloride was added and the mixture was washed successively with water, dilute acid and dilute base. Concentration of the solution left an oil which, when chromatographed (1:1, CH_2Cl_2:acetone), gave 0.83g, (70%) of 65; ^{1}H:NMR 7.4 (4H, ABq., J = 12 Hz), 4.4 (1H, m), 4.0 (2H, m) 3.6-3.0 (2H, m), 2.5 (3H, s), 2.0 (3H, s), 1.5 (10H, m).

R-phenylglycinol

Three methods were successful for the reduction of R-(-)-phenylglycine to R-(-)-phenylglycinol, each in overall yields of about 40% after recrystallization (benzene). Direct reduction was successful with BH_3:Me_2S in THF.[53b] In contrast to a literature[53e] report no reaction occurred between lithium aluminum hydride (LAH) and R-phenylglycine in diethyl ether at reflux. Sodium borohydride reduction of the ethyl ester hydrochloride was successful.[53a] LAH did reduce the ethyl ester[53c] obtained by reaction of thionyl chloride with the amino acid in ethanol followed by neutralization of the hydrochloride at low temperature.[53c]

Triethyl phosphono acetate

This reagent was prepared by the method of House[64] in 65% yield from ethylbromoacetate; b.p. 103-105° C (1.1 mm) (lit[64] 142-145° C, 9 mm).

4-chlorobutanal ethylene glycol acetal

This compound was prepared by protection of the Rosenmund reduction[65] product from 4-chlorobutyrl chloride as its ethylene glycol acetal in 56% yield[54]; b.p. 107 - 108° C (24.5 mm) (lit[54] 69 - 70°C 0.6 mm).

4-iodobutanal ethylene glycol acetal (67)

The method of Pleshakov[54] was employed and gave a 40% yield of the iodo compound 67 from 4-chlorobutanal ethylene acetal b.p. 74-78°C (.18 mm) (lit[54] 69 - 70°C, 0.6 mm); ^{1}H NMR: 4.90 (1H t, J = 6 Hz), 3.97 (2H, t overlapping), 3.85 (2H, t, overlapping), 3.25 (2H, t, J = 8 Hz), 1.99 (2H, m), 1.78 (2H, m).

Ethyl 6-bromo hexanoate

This electrophile was prepared in 50% yield from $\mathcal{E}$-caprolactone[66]; b.p. 80-85° C (0.95 mm) (lit[66] 82-83° C, 0.9 mm).

Ethyl 6-iodohexanoate

A solution of 7.72g (.045 mol) of NaI in 100 mL acetone was refluxed 5 hours with 8.0g (.036 mol) of the bromoester. Solvent removal, addition of 75 mL of CH_2Cl_2 and filtration gave after water wash and drying a yellow oil. Purification by chromatography (neutral Alumina) gave 6.93g (72%) of iodo compound.

Ethyl 4-iodo butyrate

This electrophile was obtained in 80% yield from ethyl 4-chlorobutyrate by the method described above for ethyl 6-iodohexanoate and using 1 hour reflux; bp. 57-60° C (1.2 mm).

2-cyano-6-oxazolo piperidine (58)

This compound was prepared (from R-(-)-phenylglycinol) by the method of Husson[51] in 40-50% yield depending upon the run after chromatography (8:2 hexane:ether) and recrystallization (hexane); mp 78-81° C (lit 81° C); MS(FI):m/z = 238; ^{1}H NMR:7.40 (5 H, m) 4.28 (1H, t, J = 8 Hz), 4.16 (1H, dd, J = 9.5, 3 Hz), 3.92 (1H, t, J = 8 Hz) 3.87 (1H, m), 3.75 (1H, t, J = 8 Hz) 2.2 - 1.55 (6H, m); ^{13}C NMR: 129.1, 128.6, 128.0, 116.3, 89.9, 73.1, 64.0, 47.5, 30.1, 28.1, 19.5.

Alkylation of oxazolidine 58 (preparation of 68)

A solution of LDA [prepared from 9.83 mL (65.9 mmol) of diisopropylamine and 26.4 mL (65.9 mmol) of 2.5M BuLi in hexane] in 60 mL of THF was cooled to -78° C under nitrogen. To this was added a solution of 7.15g (31.4 mmol) of 58[51] in 30 mL of THF over 15 min. After stirring at -78° C for 45 min, a solution of 10.58g (43.9 mmol) of the ethylene ketal of 4-iodobutanal 67 in 15 mL of the same solvent was added over 40 min. The solution was stirred at -78° C for 2.5 h and then quenched by addition of 100 mL of phosphate buffer (pH 6.2, 0.5M). The organic layer was separated and the aqueous layer extracted with 5 x 50 mL of methylene chloride. The combined organic layers were dried and concentrated to give a yellow oil. Chromatography (1:1 hexane:ether) produced 68 as a pale yellow oil (9.06g, 84%) which slowly crystallized on standing. Recrystallization from ether:petroleum ether gave white crystals, mp 68-69° C; $[\alpha]_D$ -119.3° (c=1.01); IR (neat): 2955, 2875, 2216, 1139, 1109cm^{-1}; ^{1}H NMR: 7.35 (m, 5H), 4.59 (t, 1H, J = 4.5 Hz), 4.24 (t, 1H, J = 8.5 Hz), 4.16 (dd, 1H, J = 9.2, 2.3 Hz), 4.01 (dd, 1H, J = 9.2, 4.6 Hz), 3.73 - 3.90 (m, 5H), 2.2 - 1.0 (m, 12H); ^{13}C NMR: 144.1(s), 128.7(d), 127.6(d), 127.3(d), 119.0(s), 103.9(d), 92.3(d), 74.9(t),

64.9(t), 62.4(t), 39.3(t), 34.3(t), 33.3(t), 29.6(t), 20.2(t), 18.3(t); MS(FI): m/z = 342.

Anal. Calcd. for $C_{20}H_{26}N_2O_3$: C, 70.14; H, 7.65; N, 8.18. Found: C, 70.58; H, 7.70; N, 8.18.

Decyanation of Nitrile 68 (Preparation of 69)

To a suspension of 21g (0.555 mol) of sodium borohydride in 500 mL of freshly distilled ethanol was added 18.1g (0.053 mol) of 68 in 75 mL of ethanol, dropwise with stirring over 45 min and under nitrogen. The solution was refluxed for 4 h, cooled and enough water added to dissolve the precipitate (*ca.* 300 mL). The solution was mixed with brine and extracted with methylene chloride, dried and evaporated to give a pale yellow oil. Chromatography with 20:1 CH_2Cl_2:MeOH gave 13.84g (82%) of 69; $[\alpha]_D$ -30°; IR (neat): 3392, 2940, 1142, 1129, 703 cm^{-1}; ^1H NMR: 7.40 (m, 5H), 4.83 (t, 1H, J = 4.5 Hz), 4.05 - 3.65 (m, 7H), 2.90 (m, 1H), 2.65 (m, 2H), 1.98 - 1.3 (m, 12H); ^{13}C NMR: 140.5, 128.6, 128.3, 127.5, 104.4, 67.4, 64.8, 62.0, 57.6, 43.1, 34.0, 27.9, 26.2, 25.6, 21.5, 19.6; MS(FI): m/z = 319.

(R)-4-(N-tosylpiperidin-2-yl)butanal (71)

A flame dried flask containing 80 mL of dry MeOH, 4.6g (0.0144 mol) of 69 and 1.0g of 10% Pd on carbon was stirred overnight under a hydrogen atmosphere. The solution was filtered through Celite and evaporated giving an oily solid (4.6g, 99%) which was comprised of 70 (X=H) and 2-phenylethanol. These could be separated by chromatography (10:1 EtOAc:MeOH).

Direct tosylation was carried out by adding 6.84g (35.9 mmol) of toluene sulphonyl chloride to a stirred solution of the mixture (4.43g) in 80 mL of methylene chloride and 5 mL of triethyl amine at 0° C under

nitrogen. After stirring for 3 h at this temperature the solution was allowed to warm to ambient for 0.5 h at which point 40 mL of water was added. The solution was stirred a further 5 min, the layers were separated and the organic layer was washed successively with dilute acid, dilute base, water and brine. Evaporation of the dried solution afforded a yellow oil which contained 70 and the tosylate of 2-phenylethanol,

To the crude mixture was added 30 mL of THF, 10 mL of ether and 50 mL of 1N HCl with stirring. After 5 h at room temperature, the solution was made basic with sat. $NaHCO_3$, the layers were separated, the organic layer was dried and concentrated to give a yellow oil. Flash chromatography with 5:1 hexane:EtOAc gave 3.2g (73% from 68) of 71; $[\alpha]_D$ +13.85° (c=0.26); IR (neat): 2941, 1725, 1335, 1155cm^{-1}; ^{1}H NMR: 9.74 (t, 1H, J = 1.8 Hz), 7.50 (ABq, 4H, J = 8.4 Hz), 4.05 (m, 1H), 3.76 (dd, 1H, J = 3.6, 14.3 Hz), 2.99 (ddd, 1H, J = 3.0, 12.6, 14.4 Hz), 2.49 (s, 3H), 2.40 (t, 2H, J = 7.1 Hz), 1.8 - 1.1 (m, 10H); ^{13}C NMR: 142.9, 139.0, 129.7, 127.1, 60.3, 52.6, 40.7, 33.9, 29.0, 27.5, 24.4, 21.9, 18.5; MS(FI):m/z = 309.

(S) Ethyl 6-(N-tosylpiperidin-2-yl)hex-2-enoate (72)

To a solution of 10.94 mL (0.273 mol) of BuLi [2.5M in hexane] in 75 mL of THF at 0° C was added 5.56g (24.8 mmol) of triethyl phosphonoacetate under nitrogen. After stirring for 30 min at 0° C, a solution of 5.12g (16.6 mmol) of 71 in 75 mL of THF was added dropwise over 1 h at 0° C. After stirring for 2.5 h, 10 mL of water and 40 mL of brine were added, the organic layer was separated, washed with brine, dried and evaporated to give a yellow oil. Chromatography with 5:1 petroleum ether:EtOAc gave 5.8g (92%) of 72 as a colorless oil $[\alpha]_D$ +28° (c=0.9); IR (neat): 2940, 1718, 1652, 1154, 1336cm^{-1}; ^{1}H NMR: 7.51 (ABq, 4H, J =

8.3 Hz), 6.93 (dt, 1H, J = 15.7, 6.9 Hz), 5.81 (dt, 1H, J = 15.6, 1.5 Hz), 4.20 (q, 2H, J = 7.1 Hz), 4.04 (m, 1H), 3.78 (dd, 1H, J = 12.9, 3.7 Hz), 2.98 (ddd, 1H, J = 2.5, 13.7, 13.8 Hz), 2.40 (s, 3H), 2.20 (m, 2H), 1.80- 1.0 (m, 10H), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR: 165.6, 147.6, 141.8, 137.9, 129.6, 125.9, 120.6, 59.1, 51.6, 39.5, 30.7, 28.0, 26.5, 23.8, 23.3, 20.4, 17.4, 13.2; MS(FI): m/z = 379.

Anal. Calcd. for $C_{20}H_{29}O_4S$: C, 63.29; H, 7.69; N, 3.69. Found: C, 63.18; H, 7.41; N, 3.91.

(S) 6-(N-tosylpiperidin-2-yl)hex-2-en-1-ol (73)

To a solution of 5.8g (15.3 mmol) of 72 in 150 mL of ether at 0° C was added 30.6 mL of DIBAL (1.5M in toluene) with stirring over 5 min. The mixture was stirred at 0° C for 1.5 h and then allowed to warm to room temperature for 45 min. The solution was cooled to 0° C and 90 mL of 2N HCl was added, followed by enough 6N HCl to dissolve all the solids. The organic layer was separated, washed with sat. $NaHCO_3$ solution, dried and concentrated to give an oil which was purified by chromatography with 2:1 pet ether:EtOAc. Compound 73 (4.5g, 88%) was obtained as a colorless oil, $[\alpha]_D$ +31.5° (c=0.46); IR (neat): 3470, 1600, 1335, 1153cm^{-1}; ^1H NMR: 7.50 (ABq, 4H, J = 8.2 Hz), 5.65 (m, 2H), 4.09 (d, 2H, J = 3.6 Hz), 4.03 (m, 1H), 3.75 (dd, 1H, J = 14.3, 2.5 Hz), 2.98 (ddd, 1H, J = 2.3, 11.5, 16.2 Hz), 2.45 (s, 3H), 2.05 (s, 2H), 1.65 (s, 2H), 1.51 - 1.20 (m, 8H);, ^{13}C NMR: 141.7, 138.0, 128.6, 128.4, 125.9, 62.7, 51.7, 40.0, 30.8, 27.8, 26.3, 24.8, 23.3, 20.4, 17.4; MS(+FAB): m/z = 336, 320, 238, 155, 91.

Anal. Calcd. for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.71; H, 8.63; N, 3.95.

(2S,3S,7R) 2,3-epoxy-6-(N-tosylpiperidin-2-yl)hexanol (74a)

To 180 mL of dry methylene chloride containing 4g of 3A crushed activated molecular sieves was added 1.33 mL (4.45 mmol) of distilled titanium isopropoxide and the stirred mixture was cooled to -23° C under nitrogen. Distilled (+)-DET (1.11g, 5.39 mmol) in 3 mL of methylene chloride was added followed by 5.00g (14.8 mmol) of 73 in 25 mL of the same solvent. After stirring for 30 min at -23° C, 6.1 mL (34.1 mmol) of *tert*-butyl hydroperoxide (TBHP) [5.6M in toluene] was added over 10 min. The reaction was quenched after 6 h by the addition of 10 mL of saturated aqueous Na_2SO_4 solution and allowed to warm to ambient temperature. After filtration through Celite, the layers were separated and the organic layer was combined with a fraction obtained by extraction of the Celite with boiling EtOAc. The combined organic layers were dried and concentrated to yield 7.23g of a pale yellow oil containing 74a, (+)-DET and excess TBHP. Column chromatography using 7:5 petroleum ether:EtOAc gave 4.55g of a colorless oil. Analysis of the ^1H NMR spectrum of the (+)-MPTA ester indicated a de of 92%. The diastereomers could not be separated by chromatography. $[\alpha]_D$ +18.3° (c=1.2); IR (neat): 3430, 2938, 1330, 1153cm^{-1}; ^1H NMR: 7.50 (ABq, 4H, J = 8.4 Hz), 4.03 (m, 1H), 3.89 (ddd, 1H, J = 2.4, 3.0, 2.6 Hz), 3.75 (dd, 1H, J = 14.0, 1.3 Hz), 3.62 (m, 1H), 3.07 - 2.87 (m, 3H), 2.40 (s, 3H), 1.98 (m, 1H), 1.81 - 1.10 (m, 12H); ^{13}C NMR: 142.8, 138.9, 129.6, 126.9, 61.7, 55.8, 52.8 [52.5], 40.6, 31.6, 29.3, 27.4, 24.2, 22.9, 21.4, 18.4.

(2R,3R,7R) 2,3-epoxy-6-(N-tosylpiperidin-2-yl)hexanol (74b)

To a stirred mixture of 50 mL of methylene chloride, 0.55 mL (1.8 mmol) of $Ti(^iPrO)_4$ and 300 mg of powdered activated 3A molecular sieves was added 0.44g (2.13 mmol) of (-)-DET in 3 mL of methylene chloride at

-35° C under nitrogen. Alcohol 73 (1.1 g, 3.3 mmol) in 10 mL of methylene chloride was added and the solution was aged 20 min at -35° C.[48] TBHP (1.35 mL of a 5.6M solution in toluene, 7.6 mmol) was added over 5 min. After stirring for 6 h at -35° C, 6 mL of ether was added followed by 2 mL of sat. Na_2SO_4 solution. The mixture was stirred for 1.5 h at room temperature, filtered through Celite and the Celite was washed with ether. The orange Celite pad was extracted with boiling EtOAc and the combined organic solutions were concentrated to afford the crude product, contaminated with (-)-DET and excess TBHP. This was chromatographed using 7:5 petroleum ether:EtOAc to give 0.92g (80%) of a white solid which was recrystallized from petroleum ether:EtOAc to give 74b, Analysis of ^1H NMR spectra of (+)-MTPA ester indicated a de of 91% before and after recrystallization, mp 88-89° C; $[\alpha]_D$ +54.19° (c=0.62); IR ($CHCl_3$): 3506, 2934, 1323, 1152cm^{-1}; ^1H NMR: 7.48 (ABq, 4H, J = 10 Hz), 4.04 (m, 1H), 3.89 (ddd, 1H, J = 1.9, 5.6, 11.3 Hz), 3.76 (dd, 1H, J = 3.5, 14.2 Hz), 3.64 (m, 1H), 3.07 - 2.89 (m, 3H), 2.45 (s, 3H), 1.8 - 1.1 (m, 12H); ^{13}C NMR: 142.8(s), 138.9(s), 129.6(d), 126.9(d), 61.8(t), 58.3(d), 55.8(d), [52.8] 52.5(d), 40.6(t), 31.1(t), 29.2(t), 27.4(t), 24.2(t), 22.7(t), 21.5(q), 18.4(t).

Anal. Calcd. for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.69; N, 3.96. Found: C, 61.40; H, 7.77; N, 3.87.

Benzylation of 74a to 75a

To a stirred suspension of 0.103g (4.3 mmol) of oil-free sodium hydride in 45 mL of THF was added 1.155g (3.3 mmol) of 74a in 20 mL of THF under nitrogen. After stirring for 15 min at room temperature, 0.735g (4.3 mmol) of benzyl bromide was added and the mixture was stirred a further 20 h at ambient temperature. Careful addition of 15

mL of water followed by phase separation, drying of the organic material and concentration produced a crude yellow oil which was chromatographed using 2:1 petroleum ether:EtOAc to give 75a as a colorless oil (1.295g, 89%); $[\alpha]_D$ +17.2° (c=0.36); IR (neat): 2938, 1490, 1332, 1154cm^{-1}; ^{1}H NMR: 7.50 (ABq, 4H, J = 8.6 Hz), 7.35 (m, 5H), 4.57 (ABq, 2H, J = 11.9 Hz), 4.04 (m, 1H), 3.80 - 3.68 (dd, 2H, J = 3.3, 11.3 Hz, partially overlapping a dd, J = 3.4 Hz), 3.46 (dd, 1H, J = 11.3, 5.7 Hz), 3.05 - 2.86 (m, 2H), 2.80 (m, 1H), 2.40 (s, 3H), 1.7 - 1.05 (m, 12H); ^{13}C NMR: 142.8(s), 139.0(s), 138.0(s), 129.7(d), 128.5(d), 127.8(d), 127.0(d), 73.3(t), 70.5(t), 56.9(d), 56.0(d), 52.8(d) [52.6], 40.7(t), 31.5(t), 29.4(t), 27.5(t), 24.3(q), 23.1(t), 21.5(t), 18.5(t).

Benzylation of 74b to 75b

In the same manner as described above for 74a, alcohol 74b was converted into benzyl ether 75b (92%); $[\alpha]_D$ +42.58° (c=0.62); IR (neat): 2938, 1332, 1154, 1094cm^{-1}; ^{1}H NMR: 7.50 (ABq, 4H, J = 8.7 Hz), 7.30 (m, 5H), 4.58 (ABq, 2H, J = 11.9 Hz), 4.01 (m, 1H), 3.80 - 3.67 (dd, 2H, J = 3.3, 11.4 Hz) partially overlapping a dd J = 3.5 hz), 3.46 (dd, 1H, J = 5.7, 11.4 Hz), 3.05 - 2.90 (m, 2H), 2.79 (m, 1H), 2.40 (s, 3H), 1.8 - 1.0 (m, 12H); ^{13}C NMR: 142.9(s), 139.1(s), 138.1(s), 129.7(d), 128.5(d), 127.6(d), 127.0(d), 73.4(t), 70.5(t), 56.9(d), 56.1(d), 52.6(d) [52.8], 40.7(t), 31.3(t), 29.3(t). 27.6(t), 24.4(q), 22.9(t), 21.6(t), 18.5(t).

(4R,10R,11R) 4-(1-hydroxy-2-benzyloxyethyl)quinolizidine (76a)

To 1.7g (3.84 mmol) of 75a in 50 mL of DME was added a sodium naphthalenide solution [0.982g (7.69 mmol) of naphthalene and 0.177g (7.68 mmol) of sodium in 125 mL of DME which was stirred 1 h after the solution turned green] over 15 min at -60° C under nitrogen. After

stirring 1 h at -60° C, 2 mL of water was added. The organic layer was then washed with brine, dried and concentrated. The resulting oily solid contained naphthalene which was removed by chromatography through a plug of silica gel using petroleum ether as eluant. The concentrated methanol extracts of the chromatography were separated on preparative TLC with 9:0.3:0.15 $CHCl_3$:MeOH:NH_4OH. The major product 76a was isolated as a colorless oil (0.41g, 35%) and the minor product (77?) as a pale yellow oil (47 mg, 4%). The spectroscopic data for 76a follows: $[\alpha]_D$ +27.31° (c=0.52); IR (neat): 3428, 2929, 2796, 1099cm^{-1}; ^{1}H NMR:7.30 (m, 5H), 4.56 (ABq, 2H, J = 12 Hz), 4.23 (m, 1H), 3.54 (dd, 1H, J = 7.3, 9.6 Hz), 3.41 (dd,1 H, J = 4.5, 9.5 Hz), 3.31 (bd, 1H, J = 11.3 Hz), 2.12 (m, 1H), 1.97 (m, 1H), 1.79 (ddd, 1H, J = 11.9, 11.6, 2.3 Hz), 1.7 - 1.1 (m, 12H); ^{13}C NMR: 138.3(s), 128.4(d), 127.6(d), 127.7(d), 73.5(t), 72.3(t), 67.8(d), 63.1(d), 62.7(d), 50.9(t), 34.4(t), 33.3(t), 26.6(t), 24.7(t), 24.3(t), 23.3(t); MS(FI): m/z = 289.

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.83. Found: C, 74.89; H, 9.07; N, 4.45.

The spectroscopic data for 77 were as follows; ^{1}H NMR: 7.34 (m, 5H), 4.56 (ABq, 2H, J = 12 Hz), 4.32 (m, 1H), 3.52 (m, 2H), 3.30 (m, 2H), 3.11 (s(b), 1H), 2.79 (m, 1H), 1.8 - 1.4 (m, 12H); MS(FI): m/z = 289.

(4S,10R,11S) 4-(1-hydroxy-2-benzyloxyethyl)quinolizidine (76b)

In the same manner as described above for 76a, 76b was obtained (70%) from 75b as white crystals, mp 74-75° C (from petroleum ether) (tlc solvent 9:1.0:0.4 $CHCl_3$:MeOH:NH_4OH); $[\alpha]_D$ +8.13° (c=0.8); IR (KBr): 3190, 2932, 2849, 1126cm^{-1}; ^{1}H NMR: 7.34 (m, 5H), 4.57 (ABq, 2H, J = 12.1 Hz), 4.24 (m, 1H), 3.50 (d of ABq, 2H, J = 9.3, 9.6 Hz), 3.05

(m, 1H), 2.92 (m, 1H), 2.79 (m, 1H), 2.56 (m, 1H), 1.8 - 1.3 (m, 12H); ^{13}C NMR: 138.0(s), 128.4(d), 127.7(d), 73.4(t), 72.3(t), 67.1(d), 56.9(d), 56.3(d), 49.4(t), 29.1(t), 27.6(t), 23.4(t), 22.7(t), 21.8(t), 19.3(t); MS(FI): m/z = 289.

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.83. Found: C, 74.66; H, 9.31; N, 4.68.

(4R,10R,11R) 4-(1,2-dihydroxyethyl)quinolizidine (78a)

To a solution of 5 mL of glacial acetic acid and 5 ml methanol containing 0.105g (0.363 mmol) of 76a was added 35 mg of 10% Pd on carbon and this mixture was stirred under an hydrogen atmosphere for 24 h. The mixture was filtered through Celite and concentrated, the residue taken up in ether and the ether solution washed with 3 x 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous layers were then concentrated to dryness, taken up in 20 mL of ether, combined with the ether from the washing, dried and evaporated to afford 78a as a colorless oil (71 mg), 98%) which was pure according to tlc analysis (9:0.4:0.8 $CHCl_3$:MeOH:NH_4OH); $[\alpha]_D$ +10.0° (c=0.26); IR (neat): 3380, 2929, 2856, 1100cm^{-1}; ^1H NMR: 4.21 (bs, 2H), 4.07 (m, 1H), 3.63 (dd, 1H, J = 7.7, 11.2 Hz), 3.41 (dd, 1 H, J = 3.7, 11.1 Hz), 3.34 (bd, 1H, J = 11.3), 2.09 (m, 1H), 1.97 (m, 1H), 1.80 (m, 1H), 1.7 - 1.1 (m, 12H); ^{13}C NMR: 69.6(d), 64.7(t), 64.3(d), 63.2(d), 51.0(t), 33.8(t), 32.8(t), 26.1(t), 24.5(t), 24.3(t), 23.3(t); MS(FI): m/z = 199.

(4S,10R,11S) 4-(1,2-dihydroxyethyl)quinolizidine (78b)

In a manner similar to that described above for the preparation of 78a, 78b was obtained as a colorless oil (97%) which was pure according to tlc analysis; $[\alpha]_D$ -2.29° (c=0.7); IR (neat): 3360, 2932, 2861, 1033cm^{-1}; ^1H NMR: 4.09(m, 1H), 3.78(dd, 1H, J = 4.9, 10.7 Hz), 3.57 (dd,

1H, J = 8.6, 10.7 Hz), 3.13 (bs, 2H), 2.73 (bd, 1H, J = 4.1 Hz), 2.58 (bd, 1H, J = 11.5 Hz), 1.9 - 1.3 (m, 12H); ^{13}C NMR: 68.2(t), 65.4(d), 65.0(d), 52.9(d), 48.4(t), 29.7(t), 25.3(t), 24.0(t), 20.5(t), 20.4(t), 19.6(t); MS(FI):m/z = 199.

Catalytic Experiments

GENERAL

For each catalytic reaction conducted the work-up of the products was the same. Thus the phrase "standard work-up" refers to the following procedure. Saturated ammonium chloride solution (20 mL) was added to the reaction mixture at 0^{o} C and the phases were separated. The aqueous phase was then extracted with 20 mL of diethyl ether and the combined organics were washed with 50 mL of 1 M HCl solution. The organics were dried and concentrated yielding colorless oils containing unreacted benzaldehyde, benzyl alcohol and 1-phenyl-1-propanol.

The catalysts, 76a and 76b, were recovered in quantitative yield by adding solid NaOH to the HCl washings until neutral, saturating with NaCl, extraction with diethyl ether, drying and concentration.

The catalysts 78a and 78b were recovered by neutralizing the aqueous layers as outlined above followed by concentration and extraction, of the resulting solids, with diethyl ether, drying and concentration.

Chromatography utilized silica gel 60 with 10:1 hexanes: Ether (diethyl) as eluent. Toluene was distilled from sodium under nitrogen. Benzaldehyde was distilled and stored under nitrogen. Diethylzinc (1.1 M in toluene) was used as obtained from Aldrich. Gas chromatography was run on a Varian Model 3700 using a 20% SE 30 column. The MTPA-Cl was prepared as outlined in the literature.[6b]

General procedure for enantioselective addition of diethylzinc to benzaldehyde using the lithium salt of 76a or 76b as the catalyst.

To a solution of 0.118g (0.408 mmol) of 76a in 28 mL of toluene was added 0.165 mL (0.408 mmol) of BuLi (2.5 M in hexanes) at 0° C. After 15 minutes 0.83 mL (8.17 mmol) of benzaldehyde was added followed by 8.91 mL (9.80 mmol) of diethylzinc (1.1M in toluene) at 0° C. After two hours at 0° C the reaction was allowed to stir at ambient temperature for 23 hours at which point gas chromatography indicated nearly complete conversion of the benzaldehyde. Standard work-up yielded a product mixture which analysis indicated to be 98% 1-phenyl-1-propanol, 1% unreacted benzaldehyde, and 1% benzyl alcohol. Column chromatography afforded 0.90g (81%) of pure 1-phenyl-1-propanol $[\alpha]$ = 37.9. (c=5.15, $CHCl_3$), 84% ee by analysis of the ^1H and ^{19}F spectra (δ = 6.18, 6.44 ppm) of the corresponding Mosher esters.[57] The percent enantiomeric excess calculated using the specific rotation of the 1-phenyl-1-propanol product was found to agree with this value. The ^1H NMR data for the 1-phenyl-1-propanol and its MTPA ester were found to be in agreement with literature values.[57]

The reaction in which 76b was used as a catalyst was identical except the reaction was stirred 432 hrs. at ambient temperature. The progress of the reaction was monitored by gas chromatography and was allowed to proceed until the reaction appeared to stop. The product mixture consisted of 3% recovered benzaldehyde 12% benzyl alcohol and 85% 1-phenyl-1-propanol. Column chromatography afforded 0.67g (60%) of pure 1-phenyl-1-propanol, 38% ee by analysis of the ^1H and ^{19}F spectra of the corresponding Mosher ester.[57]

General procedure for enantioselective addition of diethylzinc to benzaldehyde using the zinc salt 76a or 76b as the catalyst.

To a solution of .026g (.09 mmol) 76a in 7 mL of toluene was added .082 mL (.09 mmol) of $Zn(Et)_2$ (1.1 M in toluene) and the solution was refluxed for 30 minutes. After cooling to 0° C .18 mL (1.8 mmol) of benzaldehyde was added followed by 1.97 mL (2.16 mmol) of $Zn(Et)_2$ (1.1 M in toluene) and the solution was stirred 1 hour at 0° C followed by 80 hours at ambient temperature. Standard work-up yielded a product mixture which gas chrromatographic analysis indicated to be 72% 1-phenyl-1-propanol, 24% benzaldehyde and 4% benzyl alcohol. Column chromatography yielded 0.13g, (52%) of pure 1-phenyl-1-propanol, (32% ee by analysis of the ^1H NMR and ^{19}F spectra of the Mosher esters.)

The reaction in which the zinc salt of 76b was utilized as a catalyst under otherwise identical conditions as 76a yielded a product mixture consisting of 70% 1-phenyl-1-propanol, 20% benzaldehyde and 10% benzyl alcohol. Column chromatography produced 0.12g, (51%) of pure 1-phenyl-1-propanol (28% ee by analysis of the ^1H NMR and ^{19}F spectra of the Mosher esters.)

General procedure for enantioselective addition of diethylzinc to benzaldehyde using the zinc salt of 78a or 78b as catalyst.

To a solution of 0.047g (.236 mmol) of 78a in 15 mL of toluene was added 0.22 mL (.236 mmol) of diethylzinc (1.1 M in toluene) and the solution was refluxed for 30 minutes. After cooling to 0° C, 0.48 mL (4.72 mmol) of benzaldehyde was added followed by 5.16 mL (5.7 mmol) diethylzinc. The reaction was stirred 1 hour at 0° C and 120 hours at room temperature. Standard work-up yielded a product mixture which

gas chromatographic analysis indicated consisted of 75% 1-phenyl-1-propanol, 23% recovered benzaldehyde and 2% benzyl alcohol. Column chromatography afforded 0.38g (59%) of pure 1-phenyl-1-propanol (55% ee by analysis of the ^{1}H and ^{19}F spectra of the Mosher esters.)

The reaction in which the zinc salt of 78b was utilized as a catalyst under otherwise identical conditions as 78a yielded a product mixture consisting of 76% 1-phenyl-1-propanol, 20% benzaldehyde and 4% benzyl alcohol. Chromatography afforded 0.40g (62%) of pure 1-phenyl-1-propanol (58% ee by analysis of the ^{1}H and ^{19}F spectra of the Mosher esters.)

CAMPHOR DERIVATIVES

Preparation of the norcamphor imine of t-butyl glycine (97)

A solution of 0.589g (5.34 mmol) of norcamphor, 0.70g (5.34 mmol) t-butyl glycinate and 5 drops of BF_3:Et_2O was refluxed in 20 mL of dry benzene with azeotropic removal of water under nitrogen for 5 h. After cooling the dried solution was concentrated to give an oil containing the crude imine. Distillation gave pure imine (0.56g, 40%) b.p. 70 - 75° C (0.15 mm.) The ^{1}H and ^{13}C NMR indicated a mixture of diastereomers which could not be separated by chromatography since the imines hydrolyzed readily. The ratio of the diastereomers was determined to be 5:1 on the basis of integration of ^{1}H NMR spectra of the methylene imine protons. The sample was stored in the freezer under nitrogen since slow decomposition occurred at room temperature. IR: 2986, 1744, 1689, 1154cm-1; ^{1}H NMR: 3.98 [4.06] (2H, ABq, J = 11.7 Hz), 2.85 [3.0] (1H, s), 2.56 [2.50] (1H, s), 2.05 [2.3] (1H, d, J = 16), 1.8 - 1.2 (m, 16H); ^{13}C NMR: 184.50, 169.78, 80.98, 55.0 [55.58], 47.4 [47.5], 42.84, 40.38,

38.57, 38.21, 37.15, 35.82, 35.14, 28.12, 27.83, 27.5, 26.34, 25.53.

Alkylation reactions of Imine 97

A solution of 0.55g (2.47 mmol) imine 97 in 3 mL THF was added slowly to a solution of 2.71 mmol of LDA [prepared by adding 1.1 mL (2.71 mmol) BuLi (2.5M in hexanes) to .274g (2.71 mmol) diisopropylamine in 3 mL THF at 0^{o} C and stirring 15 minutes at that temperature] at -78^{o} C under nitrogen. After 20 minutes at that temperature 0.464g (2.71 mmol) benzylbromide in 3 mL THF was added. The reaction was quenched after 1.5 h by the addition of 5 mL H_2O (which also caused imine hydrolysis). Drying and concentration of the organic layer afforded, after chromatography (2:1 petroleum ether:ether) 0.289g (75%) phenylalanine t-butylester. Derivatization as the Mosher amide under standard conditions (see Part I experimental) indicated a racemic mixture.

When one equivalent HMPA was added with the imine under otherwise identical conditions as above 0.33g (85%) of phenylalanine t-butylester was obtained.

When two equivalents HMPA were added with the imine under otherwise identical conditions as above 0.237g (61%) of phenylalanine t-butylester was obtained. The Mosher amide consisted of a racemic mixture regardless of the number of equivalents of HMPA added in these alkylation reactions.

Several extraneous peaks were present in the ^{1}H NMR spectrum of the crude alkylated product due to HMPA, benzylbromide, and unreacted and hydrolyzed imine. However, the 8 lines due to the glycinate methine proton were found at approximately 3.92 ppm in analogy with the camphor imine.

D-2-oxo-7, 7-dimethyl-1-vinylbicydo [2.2.1] Heptane (102)

This was prepared according to the Organic Synthesis[81] procedure in 65% yield from (+)-10-camphor-sulfonyl chloride and diazomethane[83] *via* the corresponding episulfone; colorless oil [b.p. 105 - 109°C (16 mm.)], which solidifies upon cooling; mp 63-65° C; ^{1}H NMR: 5.82 (1H, dd, J = 17.6, 1.6 Hz), 5.40 (1H, dd, J = 17.6, 1.6 Hz), 5.23 (1H, dd, J = 17.6, 1.6 Hz), 2.46 (1H, ddd, J = 18.31, 4.64, 2.23 Hz), 2.15 (1H, t, J = 3.33 Hz), 2.03 (2H, m), 1.91 (1H, d, 18.3 Hz), 1.46 (2H, m), 0.95 (3H, s), 0.94 (3H, s); ^{13}C NMR: 217.2, 132.2, 118.9, 64.1, 48.5, 43.6, 43.4, 26.9, 25.9, 20.1, 19.3.

Preparation of ethylene glycol ketal (103)

A solution of 0.50g (3.05 mmol) of olefin 102, 0.29g (4.6 mmol) of ethylene glycol and 120 mg of p-toluenesulfonic acid in 10 mL dry benzene was refluxed 4 hours with azeotropic removal of water. After cooling the solution was washed with water, saturated sodium bicarbonate solution and brine. Concentration of the dried solution yielded 0.441g (70%) of 103 as a colorless oil after silica gel chromatography (30:1 petroleum ether:Et_2O); IR: 2950, 2882, 1163, 1122cm-1; ^{1}NMR: 6.03 (1H, dd, H = 17.7, 11), 5.17 (1H, dd, J = 11, 2.1), 5.10 (1H, dd, J = 17.7, 2.2), 3.84 (4H, m), 2.17 (1H, dt, 13.64, 4.09), 1.92 (1H, m), 1.71 (3H, m), 1.49 (1H, d, 13.64), 1.27 (1H, m), 1.12 (3H, S), 0.89 (3H, S); ^{13}C NMR: 136.0, 118.0, 116.6, 65.1, 64.3, 58.8, 50.0, 45.4, 45.2, 26.7, 24.4, 20.7, 20.5; MS(FI): m/z = 208.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.95; H, 9.67. Found: C, 74.94; H, 9.62.

Preparation of hydroxy ethylene glycol acetal 104

To 0.13g (0.63 mmol) of 103 in 2.5 mL THF was added 3.78 mL (1.89 mmol, 3 equivalents) of 9-BBN at 0° C under N_2. After stirring 3 hours

at room temperature, 1 mL of EtOH was added followed by 1.0 mL 6N NaOH and 2 mL 30% H_2O_2 at 0^o C and the solution was stirred at ambient temperature overnight. After saturation with K_2CO_3 and dilution with 10 mL Et_2O the layers were separated. The aqueous layer was extracted with 5 mL Et_2O and the combined organics were dried and concentrated to give after chromatography 100 mg (72%) of 104 or a colorless oil; IR: 3420(b), 2951, 1640, 1114cm-1; ^1H NMR: 3.95 (3H, m), 3.76 (1H, m) 3.65 (2H, m), 2.0 (3H, m), 1.75 (2H, m), 1.50 (1H, m), 1.38 (1H, d), 1.3 (2H, m), 1.04 (3H, s), 0.75 (3H, s); ^{13}C NMR: 116.6, 64.1, 62.4, 60.6, 53.6, 49.3, 44.9, 44.0, 28.5, 27.0, 26.5, 20.5, 20.5; MS(FI) m/z = 226.

Preparation of 10-hydroxymethyl camphor (100)

A solution of 0.19g (0.84 mmol) of (104) in 3 mL THF and 6 mL 1M HCl was stirred 22 hours at room temperature. The solution was diluted with 15 mL Et_2O, washed successively with aqueous sodium bicarbonate and brine, then dried and concentrated to give a 100 as a colorless oil (0.11g, 70%) after chromatography with 1:1 petroleum ether:Et_2O; IR: 3417, 2958, 2885, 1735, 1051cm-1; ^1H NMR: 3.73(2H, m), 2.42 (1H, dt, J = 19, 3.2 Hz), 2.2 (1H, t, J = 4.4 Hz), 2.0 (1H, m), 1.95-1.38 (6H, m), .95 (3H, s), .91 (3H, s); ^{13}C NMR: 222.6, 61.6(s), 59.7(t), 48.0(s), 43.5(d), 43.3(t), 28.7(t), 26.9(t), 26.6(t), 20.1(q), 19.3(q); MS(FI): m/z = 182.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95. Found: C, 72.16; H, 10.07.

Preparation of hydroxy imine (101)

A solution of 41 mg (0.225 mmol) 100 and 44 mg (0.340 mmol) t-butyl glycinate[75] in 3 mL benzene was refluxed in the presence of 1 drop of

BF_3:Et_2O with a Dean-Stark water trap under nitrogen. After 12 hours the solution was cooled, dried and concentrated to give 43 mg (65%) of the imine 101 after chromatography with 2:1 petroleum ether:Et_2O followed by 2:1 Et_2O:petroleum ether; IR: 3200, 2960, 1735, 1684, 1156cm-1; ^1H NMR: 3.92 (2H, s), 3.78 (1H, ddd, J = 11.2, 4.7, 2.8 Hz), 3.65 (1H, dt, J = 11, 1Hz), 2.3 (1H, d(b), J = 16.8 Hz), 2.05-1.6 (7H, m), 1.47 (9H, s), 1.3 (1H, m), 0.92 (3H, s), 0.84 (3H, s); ^{13}C NMR: 188.0(s), 168.9(s), 81.5(s), 59.6(t), 59.3(s), 54.0(t), 48.4(s), 44.2(d), 35.7(t), 30.2(t), 28.6(t), 28.1(q), 27.3(t), 19.7(q), 19.1(q); MS(FI): m/z = 295.

General procedure for alkylation of hydroxy camphor imine (101).

In a flame dried 25 mL 3 neck round bottom flask was added 2 mL THF, 0.144g (1.4 mmol) of diisopropylamine and 0.57 mL (1.4 mmol) BuLi (2.5M in hexanes) at 0° C under N_2. This LDA solution was stirred for 20 minutes at 0° C then cooled to -78° C at which point 0.2g (0.68 mmol) of imine 101 in 1 mL THF was added. An orange enolate solution resulted. After 30 minutes 0.128g (0.75 mmol) benzyl bromide was added in 2 mL of THF at -78°C. After 2.5 hours at that temperature the reaction was quenched with 5 mL saturated NH_4Cl and diluted with 10 mL Et_2O. Separation, drying and concentration of the organic phase yielded 0.167g (64%) of the crystalline solid 105 with de = 78% after chromatography with 1.5:1 petroleum ether:Et_2O. Recrystallization from petroleum ether did not improve this value.

When 1 equivalent HMPA was added along with the imine under otherwise identical conditions as above, except reaction time of 1.5 hours, 0.217g (83%) of alkylated product 105 was obtained in 80% de.

When 2 equivalent HMPA was employed as above 0.201g (77%) of alkylated product 105 was obtained with 80% de; IR: 2958, 1735, 1154, 1684cm-1; ^{1}H NMR: 7.3 (5H, m), 3.99 [4.03] (1H, dd, J = 10.4, 3.4 Hz), 3.78 (1H, m), 3.64 (1H, m), 3.25 (1H, dd, 12, 4), 2.95 (1H, dd, J = 14, 12), 2.2 (1H, dt, 16Hz), 1.9 - 1.4 (8H, m), 1.45 (9H, s), 0.178 (3H, s), 0.80 (3H, s); ^{13}C NMR: doubling of peaks, new peaks at 138 - 128; MS(FI): m/z = 385.

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.81; H, 9.09; N, 3.64. Found: C, 74.78; H, 9.39; N, 3.57.

Aldol reaction of hydroxy camphor imine (101)

A solution of 0.1g (0.34 mmol) hydroxy imine 101 was added to a solution of LDA [prepared by adding .072g (0.71 mmol) diisopropylamine to 0.29 mL (0.73 mmol) BuLi (2.5M in hexanes) in one mL THF at 0°C and stirring 20 minutes at this temperature then 5 minutes as -78°C] and stirred 30 minutes at -78°C. A solution of benzaldehyde [.039 mL (0.38 mmol)] in 1 mL of THF was added and the mixture was stirred at -78°C for 1.5 hours. The reaction was quenched by addition of 1 mL H_2O followed by dilution with 15 mL diethyl ether. Phase separation, drying of the organics and concentration yielded the crude aldol product 106 . NMR indicated a 7:1 ratio of pairs of stereoisomers (δ = 5.30, 5.15). After chromatography (1:1, hexane:ethyl acetate) these pairs were separated into major (76 mg, 56% yield) and minor (20 mg, 15% yield) pairs of stereoisomers. The major pair appeared to be present as approximately a 2:1 ratio of stereoisomers whereas the minor pair seemed to be present in equal amounts according to the ^{1}H NMR spectra.

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APPENDIX A

The Stabilization of Sodium Hypochlorite

Submitted to CIL as a report on the projects carried out during a summer co-operative program work term.

UNIVERSITY OF WINDSOR

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

THE STABILIZATION OF SODIUM HYPOCHLORITE

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prepared by:

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800-801-956

August 31, 1987

TABLE OF CONTENTS

1 Summary

C-I-L produces sodium hypochlorite (hypo) at its Cornwall and Becancour Works by reacting chlorine with caustic soda. The hypo currently produced at both sites is of variable quality, and is not sufficiently stable to transport long distances profitably. This imposes problems for C-I-L in terms of the product's economy and viability.

The recognized species which contribute to the stability problem are transition metal ions. The metal ions are indigenous to the hypo and therefore an effective technique for controlling and overcoming this problem was sought.

The addition of metal ion sequestering agents to the hypo was found to be ineffective for improving stability. Similarly, when the pH was decreased and the hypo filtered no extra stability was obtained. Cornwall Works is considering increasing the capacity of the chlorine scrubber to provide better emergency protection. This might be done in ways which would improve the efficiency, reliability and quality of the 12% commercial grade hypo produced at minimal incremental cost to C-I-L.

Dilution studies revealed that current 12% commercial grade Cornwall hypo, when diluted with water to 7%, exhibits markedly enhanced stability. Completion of these studies may provide the specifications required for entry into the bottled (6%) household bleach market.

2 Conclusions

A clear improvement in the stability of hypo produced at Cornwall Works is observed upon dilution with distilled or potable water.

An effective decomposition inhibitor was not found.

There is no improvement in stability upon reacting hypo to a pH of 13.2 and filtering.

3 Recommendations

The following are recommended:

1. Complete the dilution study and determine the specifications required to enter the bottled (6%) household bleach market.

2. Increase the capacity of the chlorine scrubber at Cornwall Works to provide better emergency protection while also improving the efficiency and reliability of the commercial (12%) grade hypo manufacture.

4 Main Section

4.1 Background

Sodium Hypochlorite (NaOCl) is produced by C-I-L at Cornwall and Becancour Works. Present C-I-L hypo is of variable quality and not stable enough to ship long distances profitably (half-life for Cornwall is 100 days, half life for Becancour is 80 days). The hypo can be sold as a 12% commercial grade solution (a measure of its bleaching potential) used for waste water disinfection or in wood pulp bleaching, and/or as a 6% bottled household bleach. It is the latter market which C-I-L would like to enter. Development of a cost effective decomposition inhibitor, or of an inherently more stable product (with a half-life greater than 180 days) would open up broader and more profitable markets to C-I-L.

Two approaches envisaged in parallel:

1) Identify with Cornwall Works the process improvements required to manufacture sodium hypochlorite having a stability which is acceptable for a bottled household bleach.

2) Continue earlier work in search of inhibitors of hypo decomposition.

4.2 Introduction

Aqueous sodium hypochlorite is prepared, while cooling, by the reaction of chlorine gas and aqueous caustic (rxn. 1).

(1) $Cl_2 + NaOH \longrightarrow NaOCl + NaCl$

The hypo produced in this way contains 13-15% of active chlorine (indicates amount of available chlorine in units of gm/100cc of solution; industry refers to it as "Trade Percent"). Unfortunately hypo is a thermodynamically unstable species which decomposes via two possible pathways to give either chlorate ions or chloride ions. See reactions 2 and 3 respectively.

(2) $3\ NaOCl \longrightarrow NaClO_3 + 2\ NaCl$

(3) $NaOCl \longrightarrow NaCl + 1/2\ O_2$

The decomposition is accelerated to varying degrees by different catalysts. Reaction (2) is catalyzed by several sources, for example heat, and can therefore be controlled by attention to temperature. Reaction (3) is subject to mutual promotion of catalysis by trace

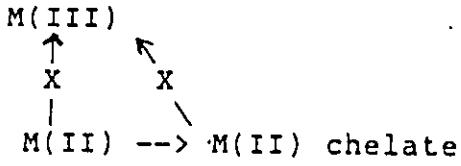
transition metals, e.g: copper, nickel, iron and cobalt, which are present in the hypo. These metals are oxidized by the hypo, from their low oxidation states, to their unstable high oxidation states where they react to give off oxygen, and are subsequently reduced to low oxidation state. This continuous redox reaction cycle eventually consumes the hypo.

4.3 Theory of Sequestering Agents Tested

The logic employed for adding sequestering agents to hypo is to stop the catalytic cycle at the low oxidation state of the metal. For example:

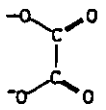
low M(II) --X--> high M(III)

By forming a metal complex or chelate compound which inhibits oxidation of the metal to the higher unstable oxidation state (and which is itself not active in the catalytic cycle), the catalytic cycle can be broken. For example:

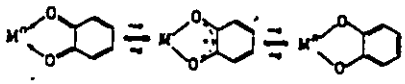


A further requirement is that the chelating ligands must resist the aggressive hypochlorite environment. Since it is known that copper ions are dissolved in the hypo, whereas nickel and iron are heterogeneous catalysts (and therefore might be negated by filtration or adsorption), particular emphasis was placed on a search for a chelate which would sequester copper. The following is a list of ligands tested, their structure and any relevant known reactions:

Table 1: Sequestering Agents Tested

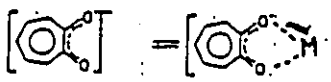
Ligand	Structure	Comment
Oxalate		- this bidentate ligand gives insoluble salts with 2^{+} cations such as Cu^{2+} (4)

Orthodihinone (catechol)



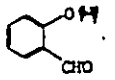
(3a)

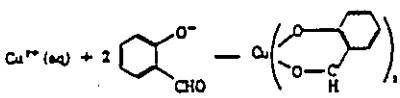
Tropolone



(3b)

Salicylaldehyde

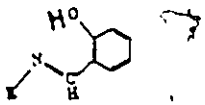


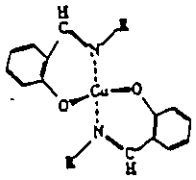


- complex insol. in aqueous soln.

(3d)

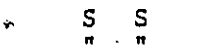
Salicylaldehyde oxime



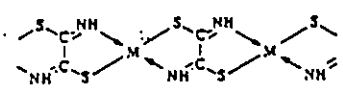


(3c)

Dithiooxamide (rubeanic acid)

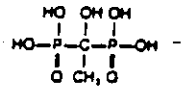


-forms insoluable polymeric complexes with Cu(II) & Ni(II)

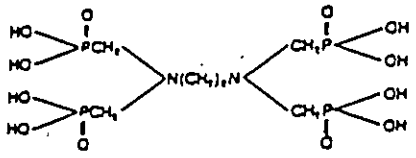


(1,2)

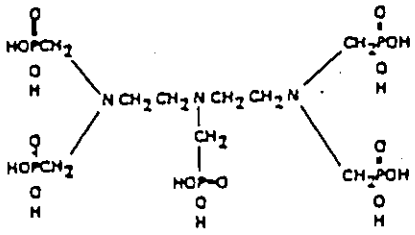
Dequest 2010



Dequest 2041

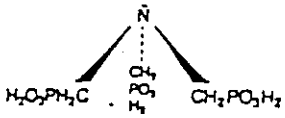


Dequest 2060



-> useful as a hydrogen peroxide stabilizing agents (5)

N-TPA



Dequest 2006

-sodium salt of N-TPA

4.4 Methods and Materials

Sodium hypochlorite (13-15% as Cl_2 w/vol) was obtained from Cornwall Works and stored in a cold room (T = 6°C) until required. In all of the experiments, the effectiveness of an additive was determined by comparing the active chlorine strength of the treated hypo before and after storage. The strength of the hypo was determined by titrimetric means (see Appendix I). In each set of experiments a control sample consisting of untreated hypo was included such that a direct comparison of the effectiveness of an additive could be made. The samples, 50 g. of hypo, were stored in amber coloured glass bottles at room temperature (24°C) with various quantities of the additives. (See Appendix II)

The theory that decreasing pH to "neutrality" might increase precipitation of metal hydroxides thereby increasing stability was tested. The effect of reducing pH was studied by bubbling chlorine gas at a constant rate through cooled hypo (10°C) with stirring to reach a determined pH. This was followed by filtering and then allowing the samples to stand. Tables of pH values are given in Appendix III and in the Results section of this report. This experimentation was carried out in an efficient fumehood.

The dilution studies involved dilution of hypo to various strengths, storing and monitoring. Appendix IV contains the tabulated results. (The results are also presented graphically in the Results section of this report.)

The decay of hypo in solution can be described by either a first order or a second order reaction - i.e. the rate of decomposition is proportional to the concentration of the surviving active chlorine or the square of that concentration, respectively. The time required for the disappearance of 50% of the original hypo is $t_{1/2}$ - the half life of the hypo. Curve fitting procedures give a better fit from the second order decay assumption than the first order. However, the differences are often small and since half life is a concept meaningful only for first order decay, all calculations are first order (see Appendix I for Equation).

4.5 Results

4.5-1 Additives

Several sets of sequestering agents were tested and the results tabulated. (See Appendix II). Table HY11 shows that 1% sodium oxalate has little effect on the normal (i.e. control sample) decomposition of hypo, whereas 1% of either catechol or Dequest 2010 accelerates the decomposition. Accelerated decomposition was observed for 1% of

Dequest 2041, 2060 and NTP-A as seen in Table HY12. Similar decomposition for 1% tropolone and dithiooxamide can be seen in Table HY13. When 10 ppm of NTP-A, Dequest 2010, 2041 and 2060, oxalate, tropolone, catechol, and 30 ppm of dithiooxamide was tested, marginal stabilization was achieved only with Dequest 2041 (see HY14 and HY14B). When combining each of the above with 1% silicate (as outlined in Tables HY15, HY15b), no improved stabilization was achieved. Dequest 2006 gave marginal stabilization without sodium silicate added. Similarly when salicylaldehyde and salicylaldoxime alone, and in combination with 1% Na_2SiO_3, were tested marginal stabilization was achieved (Table HY16) with the oxime.

4.5-2 Chlorine Addition

It appears that bubbling chlorine gas through cooled hypo to "neutrality" and letting the sample stand, causes accelerated decomposition of hypo.

Initial pH of hypo	Adjusted pH of hypo	Results
13.73	7.5	- immediate decomp. of hypo; $t_{1/2}$ = 5 min.
13.73	8.5	- as above $t_{1/2}$ = 10 min.
13.73	9.1	- accelerated decomp. $t_{1/2}$ = 2 hrs.
13.73	9.7	- gradual decomp. $t_{1/2}$ = 13 hours

A pH curve (Hypo_Cl2) was obtained (see Figure I and Appendix III). Reacting excess caustic in the hypo with chlorine gas to pH 13.2 does not give added stability, while destabilization occurs if the pH is decreased to pH 11.15.

Initial pH of hypo	Adjusted pH of hypo	Results
13.96	11.15	- $t_{1/2}$ = 26 days
13.96	13.20	- $t_{1/2}$ = 95 days

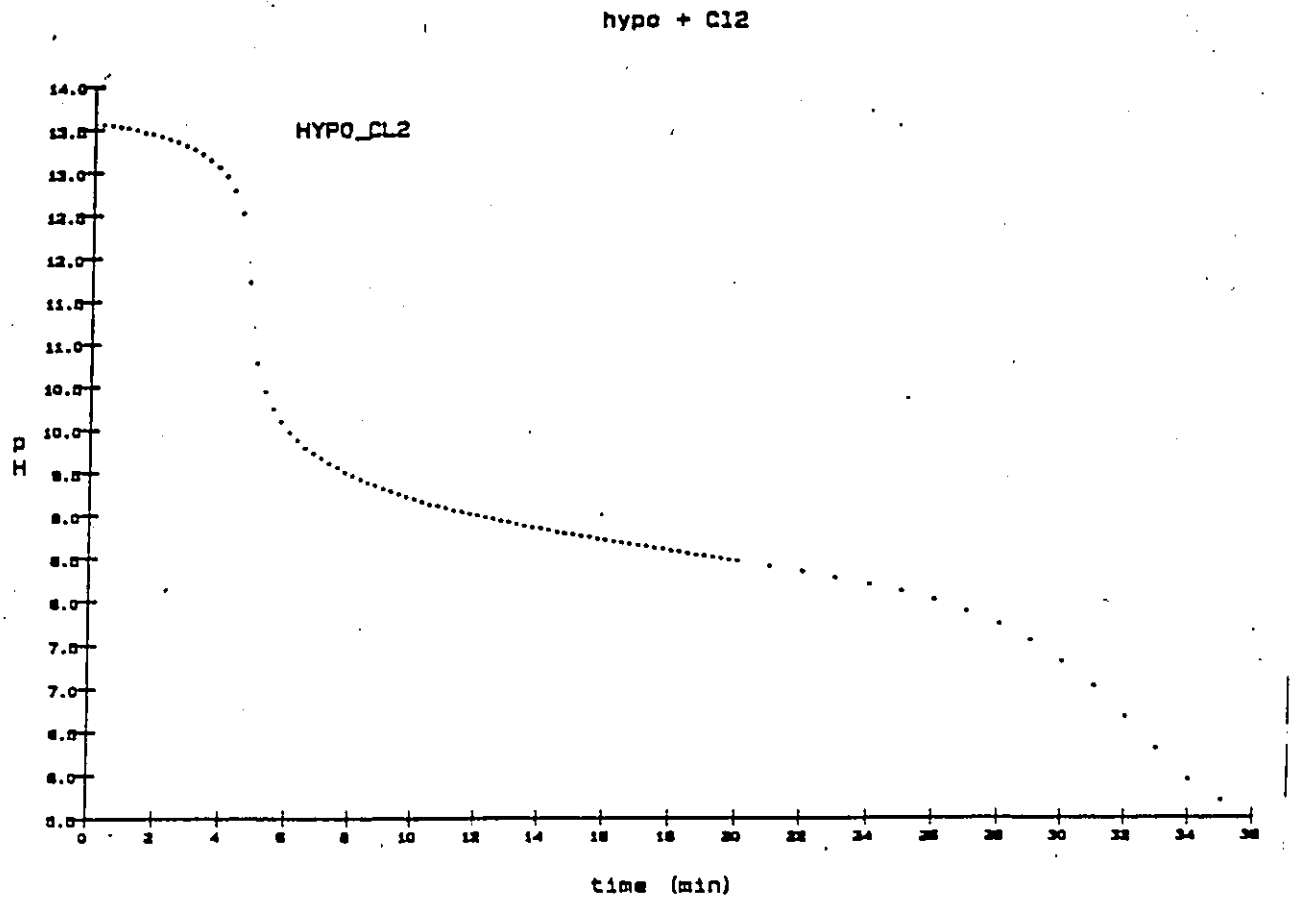


Figure I

4.5-3 Dilution Tests

In order to elucidate the effect of dilution on stability, hypo was diluted to various strengths with distilled (see Table DIL11, and DIL12) and potable (see Table DIL13) water (see Appendix IV). To date a clear improvement in stability was observed with increasing dilution of hypo. The half life of hypo increases from 100 days for concentrated hypo, to 250 days for 30% dilution (v/v), to 400 days for 50% dilution (v/v). The use of potable water versus distilled water seems to have no detrimental effect on stability. Figure II (combograph) illustrates these results.

COMBOGRAPH

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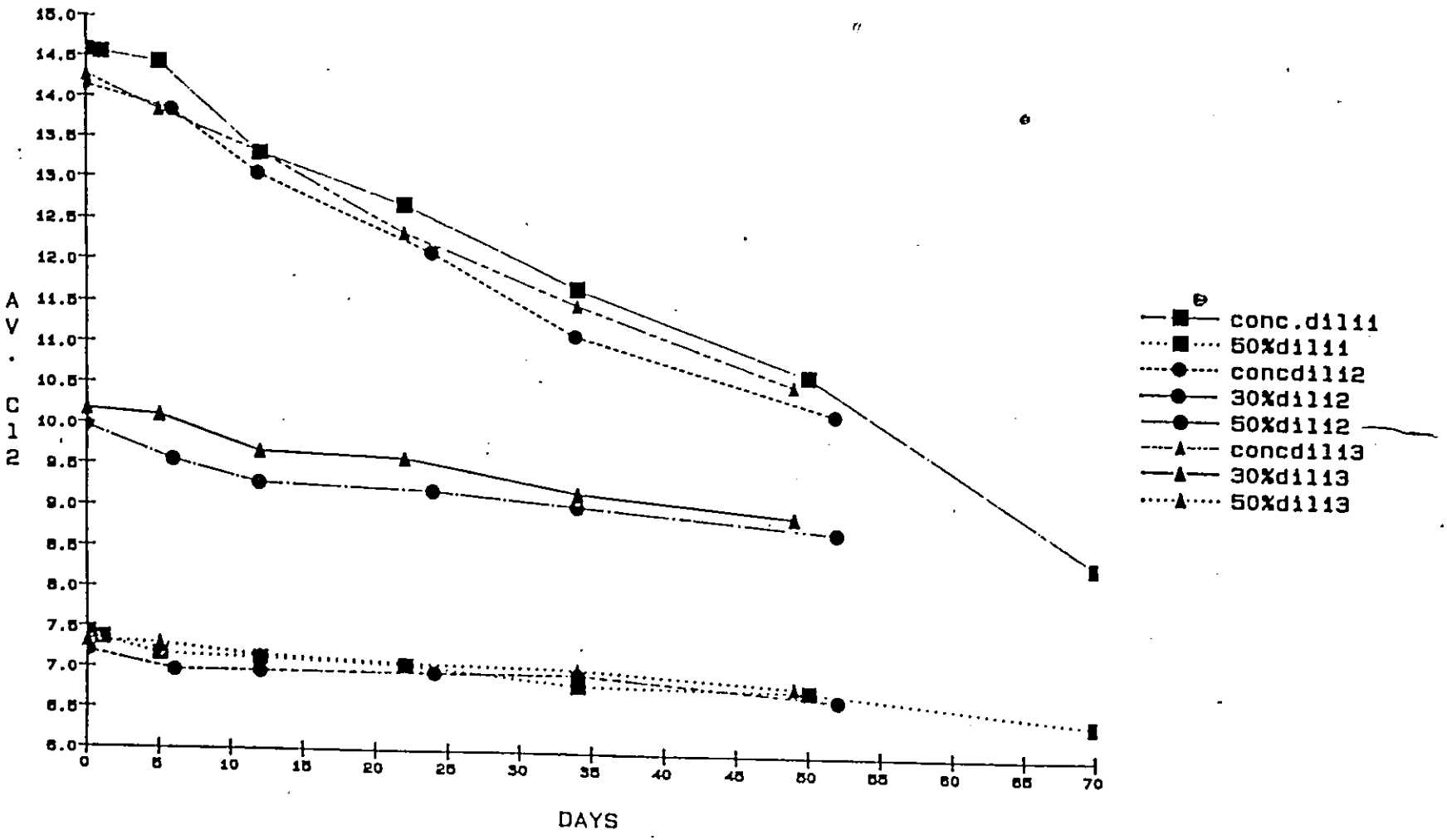
DILUTION VS STABILITY



4.6 Discussion

4.6-1 Additives

The sequestering of the low oxidation state of trace metals present in hypo is one way to break the catalytic cycle of decomposition. However, problems occur due to the strongly oxidizing conditions which are present in the hypo. Most of the sequestering agents tested are organic ligands which are subject to attack in the aggressive hypo environment. Appendix II gives the results for the additives tested. The effectiveness ranges from much accelerated decomposition, to slightly increased decomposition, to marginal stabilization. Each additive was tested alone, and in the presence of 1% m/m (mass per mass) of sodium silicate. The sodium silicate removes heterogeneous metals present (Fe, Ni) by adsorption onto their surface. This prevents the close approach of hypochlorite and the metal ions thus rendering the ions inactive.[7] In this way the ability of each additive to sequester copper could be tested and its effectiveness gauged.

In the cases where accelerated decomposition occurred visual observations (heating and bubbling hypo) confirmed a vigorous reaction between the hypo and the particular additive.

Where a slight destabilizing effect was noted no visible reaction between the ligand and the hypo was noticed, this was also the case where modest stabilization occurred.

In cases where moderate stabilization occurred optimization studies, for dosage of additives, might improve the stabilizing ability of the additive. However, even if a large increase in stability occurred the cost effectiveness of the ligand may preclude its use in large scale production. In any case the exercise does provide for expanding the knowledge as to what type of ligands are promising candidates for this task.

An effective decomposition inhibitor, when added to the present quality hypo would allow C-I-L to avoid a major capital investment in equipment (for example coolers, purer reagents and filters), to improve the quality of hypo. The alternative to additive use for stabilization of 12% hypo, is to improve the production facilities themselves. A Visit Report on Cornwall Works, in the Miscellaneous section of this report contains a suggestion on how this might be achieved at minimal incremental capital cost to C-I-L.

4.6-2 Chlorine Addition

A theory that increasing precipitation of metal hydroxides would be facilitated by decreasing the pH of hypo solutions was investigated. Filtration of the hypo and re-basification would then lead to a product devoid of most of the metals thus resulting in a more stable product. Perhaps not surprisingly, accelerated decomposition was observed as the pH was decreased. Previous authors[8] indicated that "hypo will decompose rapidly below pH = 8.0". In this instance it seems that even at a pH as high as 11.2 accelerated decomposition occurs. From Fig. I it can be seen that at pH 11.2 the gradient of the curve is largest which, in turn, implies that decomposition would be accelerated at any point along the curve in this region. This assumption is confirmed by the experimental fact that no decrease in stability occurs if the pH is kept greater than 13.2, the area just before the inflection point on the curve.

4.6-3 Dilution

Since none of the additives was found to be effective in stabilization of 12% hypo, experiments were started to see if dilution had any effect on stability. Previous authors indicated that dilute samples of hypo have longer half-lives[6]. The exact reason(s) for this is the subject of some debate. The debate centers around the question of first vs. second order decay. The most obvious explanation is that the decomposition is higher than first order in hypochlorite concentration; in this case half life is meaningless over the wide concentration ranges. Regardless, however, it is certain that decreasing metal concentration increases stability[6]. Theoretically, by diluting the hypo, the trace metals are also diluted, perhaps to the point where catalytic ability is greatly reduced. The table below supports this postulate.

Cornwall Hypo-Metal Analysis
(ppm)

metal	conc. hypo	30%	50%
Fe	.012	.084	.006
Cu	.014	.0098	.007
Ni	.008	.0056	.004
Co	.01	.007	.005
$t_{1/2}$ (days)	100	250	400

The observed half life increases as the metal ion concentration decreases. If metal dilution is a major factor in stability of hypo it may be inferred that if conc. hypo is prepared, with metal concentration ion in the range of the 30-50% hypo, then a stable conc. product could result.

The results indicate that a clear increase in stability is gained upon dilution. This being the case then there is no need to pre-stabilize the current C-I-L 12% hypo, to enter the household bleach market, since simple dilution to 6% produces stable hypo (i.e. $t_{1/2}$ > 180 days). The question of the resultant quality, compared to competitors products already in the market place, can be determined by initiating direct competition studies.

Although the dilution studies are incomplete, the trend toward increasing stabilization with increased dilution is very clear (see Figure II). At this point no differences in the stability of the hypo diluted with distilled versus potable water has manifested itself. This may mean that absolutely pure water is not essential for enhanced stability. Completion of the study will answer this question, and is therefore, highly recommended. It will be interesting to note what happens when the lines on the graph begin to cross. Will they continue with the same slope, or change as the concentration decreases to the slope of the less dilute sample? This information will be valuable in predicting the half life of C-I-L bleach from its known initial concentration.

5 References

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6 Appendices

Appendix I

Titration Method

Determination of Hypo Active Chlorine Strength

Introduction

The sample is treated with an excess of potassium iodide and acidified with 4N sulfuric acid. The liberated iodine is then titrated with standard sodium thiosulphate.

$$NaOCl + NaCl + H_2SO_4 \longrightarrow Cl_2 + NaSO_4 + H_2O$$

$$Cl_2 + 2\ I^- \longrightarrow 2\ Cl^- + I_2$$

$$I_2 + 2\ S_2O_3^{2-} \longrightarrow 2\ I^- + S_4O_6^{2-}$$

Reagents

16.5% KI
4N H_2SO_4
0.1 M $Na_2S_2O_3$
starch indicator solution

Procedure

To a solution of 50 ml of distilled water, 10 mls of 16.5% KI and 20 mls of 4N sulfuric acid is added exactly 1 ml of hypo in a 250 ml Erlenmeyer flask. This dark brown solution is swirled briefly and then titrated with 0.1N sodium thiosulphate to a light yellow colour. After adding 5 drops of starch indicator the now blue solution is titrated to a colourless end point.

Calculations

$$\text{Active chlorine (g/l)} = \frac{\text{Titre (ml)} \times 0.1 \times 35.5}{1\ \text{ml}}$$

$$\% \text{ av. chlorine} = \frac{\text{active chlorine}}{10}$$

$$= \text{trade percent}$$

Half life $t_{1/2}$

1st order

$$t_{1/2} = \frac{(\log 2)\ (T)}{\left[\log \frac{(Co)}{(Ct)}\right]}$$

T = time(days)
Co = initial av. Cl_2
Ct = final av. Cl_2

Appendix II

Additive Tables

HY11

Day	av. Cl_2 control	sodium oxalate 1 % m/m	catechol 1 % m/m	Dequest 2010 1 % m/m
0	14.58	14.58	14.58	14.58
1	14.55	14.47	.04	.27
5	14.45	14.40		
12	13.33	13.26		
22	12.73	12.41		

HY12

Day	av. Cl_2 control	Dequest 2041 1 % m/m	Dequest 2060 1 % m/m	NTP-A 1 % m/m
0	14.73	14.73	14.73	14.73
1	14.20	0.18	0.18	0.39

HY13

Day	av. Cl_2 control	tropolone 1 % m/m	dithio-oxamide 1 %m/m
0	14.32	14.32	14.32
1	14.24	3.70	6.40

HY14

Day	av. Cl_2 NTP-A 10 ppm	Dequest 2010 10 ppm	Dequest 2041 10 ppm	Dequest 2060 10 ppm	sodium oxalate 10 ppm
0	14.31	14.31	14.31	14.31	14.31
1	13.80	14.15	14.00	14.11	13.83
5	13.40	13.79	13.70	13.65	13.67
12	13.01	12.89	13.12	13.02	12.83

HY14b

av. Cl_2

Day	control	tropolone 10 ppm	catechol 10 ppm	dithio-oxamide 30 ppm
0	14.31	14.31	14.31	14.31
1	14.20	13.92	13.69	13.80
5	14.08	13.42	13.85 ?	13.56
12	13.05	12.92	12.73	13.19

HY15

av. Cl_2

day	control	*	NTP-A 10 ppm*	Dequest 2010 10 ppm*	Dequest 2041 10 ppm*	Dequest 2060 10ppm*
0	14.27	14.27	14.27	14.27	14.27	14.27
5	13.74	13.54	13.26	13.31	13.53	13.53
12	12.83	12.76	12.56	12.74	12.53	12.57
22	12.26	12.28	11.54	11.79	11.38	11.96

* = 1 % m/m of sodium silicate added

HY15b

Day	sodium oxalate 10 ppm*	tropolone 10 ppm*	catechol 10 ppm*	dithio-oxamide 30 ppm*	Dequest 2006 10 ppm	Dequest 2006 10 ppm*
0	14.27	14.27	14.27	14.27	14.27	14.27
5	13.01	13.00	13.30	13.93	13.61	13.51
12	12.41	12.64	12.78	13.03	12.87	12.84
22	11.72	11.40	11.96	11.98	11.84	12.40
34					11.55	10.92

* = 1 % m/m of sodium silicate added

HY16

Day	av. Cl_2 control	salicyl-aldehyde 10 ppm	salicyl-aldoxime 10 ppm	salicyl-aldehyde 10 ppm*	salicyl-aldoxime 10 ppm*
0	13.94	13.94	13.94	13.94	13.94
5	13.74	13.34	13.70	13.35	13.77
12	12.94	12.86	12.99	12.54	13.04
22	12.31	11.74	12.31		12.32

* = 1 % m/m of sodium silicate added

Appendix III

HYPO_CL2

Cl2 + hypo

0	1 time (min)	2 pH	0	1 time (min)	2 pH
1	0.00	13.65	53	13.00	8.99
2	0.25	13.64	54	13.25	8.97
3	0.50	13.63	55	13.50	8.95
4	0.75	13.61	56	13.75	8.93
5	1.00	13.60	57	14.00	8.92
6	1.25	13.58	58	14.25	8.90
7	1.50	13.55	59	14.50	8.88
8	1.75	13.53	60	14.75	8.86
9	2.00	13.50	61	15.00	8.85
10	2.25	13.47	62	15.25	8.83
11	2.50	13.44	63	15.50	8.82
12	2.75	13.39	64	15.75	8.80
13	3.00	13.35	65	16.00	8.78
14	3.25	13.30	66	16.25	8.76
15	3.50	13.23	67	16.50	8.75
16	3.75	13.15	68	16.75	8.74
17	4.00	13.04	69	17.00	8.72
18	4.25	12.88	70	17.25	8.71
19	4.50	12.61	71	17.50	8.69
20	4.75	11.80	72	17.75	8.68
21	5.00	10.86	73	18.00	8.66
22	5.25	10.52	74	18.25	8.65
23	5.50	10.32	75	18.50	8.63
24	5.75	10.17	76	18.75	8.61
25	6.00	10.05	77	19.00	8.60
26	6.25	9.95	78	19.25	8.59
27	6.50	9.87	79	19.50	8.57
28	6.75	9.80	80	19.75	8.56
29	7.00	9.74	81	20.00	8.54
30	7.25	9.68	82	21.00	8.48
31	7.50	9.63	83	22.00	8.42
32	7.75	9.58	84	23.00	8.35
33	8.00	9.53	85	24.00	8.27
34	8.25	9.49	86	25.00	8.19
35	8.50	9.45	87	26.00	8.09
36	8.75	9.42	88	27.00	7.96
37	9.00	9.38	89	28.00	7.81
38	9.25	9.35	90	29.00	7.62
39	9.50	9.32	91	30.00	7.38
40	9.75	9.29	92	31.00	7.10
41	10.00	9.26	93	32.00	6.75
42	10.25	9.23	94	33.00	6.38
43	10.50	9.20	95	34.00	6.02
44	10.75	9.18	96	35.00	5.78
45	11.00	9.16			
46	11.25	9.13			
47	11.50	9.11			
48	11.75	9.09			
49	12.00	9.07			
50	12.25	9.05			
51	12.50	9.03			
52	12.75	9.01			

Appendix IV

DIL11

DILUTION TEST (DISTILLED WATER)

DAY	CONC. HYPO	50% DIL. v/v
0	14.58	7.43
1	14.55	7.37
5	14.45	7.18
12	13.33	7.15
22	12.73	7.07
34	11.75	6.85
50	10.72	6.82
70	8.43	6.44

DIL12

DAY	CONC. HYPO	30% DIL. v/v	50% DIL. v/v
0	14.15	9.97	7.21
6	13.85	9.57	6.98
12	13.08	9.30	6.98
24	12.14	9.23	6.98
34	11.17	9.07	6.98
52	10.24	8.79	6.71

DIL13

DILUTION TEST (POTABLE WATER)

DAYS	CONC HYPO	30% DIL. v/v	50% DIL. v/v
0	14.27	10.17	7.34
5	13.85	10.11	7.31
12	13.34	9.68	7.18
22	12.38	9.62	7.10
34	11.55	9.23	7.05
49	10.60	8.97	6.87

II Miscellaneous

1. Summary

This section of the report contains 3 parts:

The first part contains the results of an experiment to determine the stability of a chemical tanker lining toward 50% diaphragm grade caustic. A covering letter and brief report were written.

In the second part the results of a literature search on the possibility of scrubbing vent gas containing CS_2 with sodium hypochlorite is given. A summary report and covering letter are given.

Finally, a Visit Report to Cornwall Works was written after a tour of the sodium hypochlorite manufacturing facility.

C-I-L Reasearch Centre
2101 Hadwen Road, Sheridan Park
Mississauga, Ontario L5K 2L3
July 14, 1987

c.c. C.M. Davidson

From: Luca C. Matassa

To : Gordon Churchill
Sulphur Products
North York

Ref : RID/CL1-50-04

Chemical Tanker Lining Stability Against Caustic

In response to your memo of June 24, 1987, to Martin Davidson, we have conducted an experiment to test the stability of chemical tanker lining towards 50% diaphragm grade caustic.

Overall it appears that the physical properties (colour, texture, brittleness) of the lining are unchanged when immersed for 7 days at 38°C. Some degradation, albeit minor, of the lining is evidenced by a deposit of a powdery substance in the reaction flask.

Attached is a summary which includes a fuller description of the procedure and information obtained.

Luca C. Matassa

Luca C. Matassa

Attach.
105.26

TANKER LINING STABILITY AGAINST 50% DIAPHRAGM CAUSTIC

PURPOSE

The purpose of this investigation is to determine if immersion of chemical tanker lining in 50% diaphragm grade caustic for 7 days at 38°C has any effect on its physical properties.

PROCEDURE

Two chips of the lining were immersed in 60 mls of caustic and the resultant suspension was placed into a temperature controlled water bath (38°C) for 7 days. A blank consisting of caustic only was also immersed in the bath.

After 7 days the chips were removed from the bath, washed with water and allowed to dry.

OBSERVATIONS

Before Immersion

The front face of each chip was dark brown in colour, the sides were white or brown (from rust) and both possessed iron oxide coating on their obverse sides. A small portion of each chip was removed prior to immersion for use as a control.

mass chip #1 = .3973 gm
mass chip #2 = .1007 gm

Each chip possessed a smooth front face and was brittle in nature. The caustic utilized was clear and colourless.

After Immersion

The front face remained identical in colour to the control whereas the obverse side (iron oxide coating) became more red-brown in colour. The smooth texture and the brittleness of the lining was retained. A small deposit of a white powdery substance visible at the bottom of the flask accompanied a weight loss.

mass chip #1 = .3930 gm (-.0043 gm; 1.0%)
mass chip #2 = .0976 gm (-.0031 gm; 3.0%)

The test caustic was very pale yellow in colour whereas the control caustic was still colourless.

CONCLUSION

It appears that immersion in 50% caustic has little effect on the physical properties of chemical tanker lining.

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c.c. E.W. Lucht, Cornwall
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L.C. Matassa, Res. Ctr

May 22, 1987

From: C.M. Davidson

To : M.C.F. Rogers
MEOH
North York

Ref : RID/File SC4-43-07

Scrubbing Carbon Disulfide Vent Gas

In response to your memo of 28 April we have carried out a brief literature survey to determine whether the reaction between carbon disulfide and sodium hypochlorite might be a suitable basis for a vent gas scrubbing technique.

The answer seems to be a qualified 'yes'. Work on what seems to be coal gas cleaning (dating from the 1920s) suggests that up to 67% removal of carbon disulfide can be achieved by countercurrent scrubbing with hypochlorite in a packed tower. Whether the incomplete removal is due to inherently poor kinetics or to poor column design is not clear from the literature. The reaction products are carbonate, sulfate, carbon tetrachloride and chloroform (the last two should give us pause).

I attach a fuller description of the information obtained, including some column design data. I hope this answers your questions, at least initially.

Martin Davidson/DJD

Martin Davidson

Attach.
104.11

REACTION BETWEEN CS_2 AND NaOCl: Literature Survey

The Two Questions Addressed Are:

1) Does CS_2 react with NaOCl?

2) If so, under what conditions and to what extent?

Summary

The removal of CS_2, present either in a gas stream or in a solution phase; can be at least partially realized utilizing a NaOCl solution.

In tests[1,2] for CS_2 removal from commercial gas with NaOCl solutions, a maximum of 67% removal was achieved.

Waterman and Heimal[3] completely removed CS_2 from oil with NaOCl. Wood, Lowy, and Faragher[4] showed that NaOCl solutions oxidize naptha solutions of CS_2 to Na_2CO_3 and $NaSO_4$ .In a continuation of that study Wood ,Greene, and Provine[5] partially removed CS_2 using various strengths of NaOCl.

The Removal of CS_2 Preseent in Gas Stream

Tests were conducted on removing CS_2 with NaOCl solution from commercial gas. Removal of CS_2 varied directly with contact of CS_2 and absorbant. Removal as high as 46% was achieved (Table 1). A reasonable variation in the amount of NaOCl in solution has little effect on removal. Increasing the temperature of hypo to 100°C gave much poorer efficiencies. Adding catalytic materials (15 g/l Ni_2O3, ZnNO, Fe_2O_3) gave no appreaciable increases. To obtain the most intimate contact of gas and absorbant the gas was washed by passing it through a series of three absorption towers. The towers (27 in. high by 2 in. in diameter) were packed with pebbles and arranged in a cascade, the liquor flowing over the pebbles counter current to the flow of gas.

Table 1

Fixed sulphur compounds in gas before scrubbing, grains per 100 cu. ft.	10.01
Fixed sulphur compounds in gas after scrubbing, grains per 100 cu. ft.	5.4
Per cent sulphur removed	46.0
Volume of gas passed through, cubic feet	4.2
Rate of passage of gas, cubic feet per hour	0.364
Available chlorine before absorption, grams per liter	0.56
Available chlorine after absorption, grams per liter.	0.575
Volume of absorbent, liters	4.0
Rate of flow of absorbent, liters per hour	6.0
Amount of chlorine consumed, grams	1.14
Grams sodium hydroxide per liter	0.234
Volume of gas used for sulphur analysis before absorption, cubic feet	3.796
Volume of gas used for sulphur analysis after absorption, cubic feet	3.413

In subsequent work[2] a removal of 67% of CS_2 (Table 2) from commercial gas was achieved. Greater amounts could be removed if the CS_2 flow rate was decreased or the tower enlarged. The hypochlorite tower was a glass tube 2 in. in diameter and 44 in. long packed for a length of 36 in. with evenly sized metallurgical coke about 1/2 in. in diameter. The NaOCl solution was allowed to flow from an overhead reservoir steadily down over the coke filling in the tower. The gas under test flowed upwards through the wettted coke filling. The alkaline NaOCl reacts with CS_2 to form a carbonate and a sulfate as well as carbon tetrachloride and chloroform. The objection to the use of hypo for CS_2 removal by this method is the introduction of chlorine compounds into the commercial gas.

Table 2

Run number	I	II	III
Total sulphur in raw gas Grains / 100 cu. ft.	7.0	6.1	5.2
Total sulphur as hydrogen sulphide Grains / 100 cu. ft.	2.4	1.3	1.5
Total sulphur as organic sulphur Grains / 100 cu. ft.	4.6	4.8	3.7
Total sulphur in purified gas Grains / 100 cu. ft.	1.9	1.6	1.4
Per cent of organic sulphur removed by tower	59.0	67.0	62.0
Available chlorine before absorption Grams / Liter	2.2	5.5	4.34
Available chlorine after absorption Grams / Liter	1.0	4.6	3.8
Volume of absorbent, Liters	12.0	19.0	18.0
Gas Purified, Cubic feet	6.125	10.0	9.20
Rate of passage of gas through tower Cu. feet / Hour	0.756	0.650	0.715

The Removal of CS_2 Present in a Solution Phase

The complete removal of CS_2 from an oil was accomplished[3] using the following procedure. About 50 cc of the oil containing CS_2 was shaken for several hours with 250 cc of .6 N NaOCl solution. The oil was then worked several times with a solution of sodium carbonate and with water and filtered 3 times through 2 cm of bauxite. The degree of alkalinity of the hypo was not indicated.

Hypo containing 5.25% active Cl_2 oxidized naptha solutions of CS_2 to sodium carbonate and sodium sulfate. The alkalinity of the hypo was not indicated.[4]

$$CS_2 + 8NaOCl + 6NaOH \longrightarrow 2Na_2SO_4 + Na_2CO_3 + 8NaCl + 3H_2O$$

Partial removal of CS_2 in naptha solutions was achieved by shaking with hypo solutions of various strengths of alkalinity and available chlorine content (Table 3).[5]

Table 3

hypo soln.	I	II	III
alkalinity %	.29	.62	1.68
av. Cl_2 %	5.63	11.03	5.42
% S* as CS_2	.2	.16	.19

*-initial %S in stock soln. = .28

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103.61

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